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β-Lactamase Characterization of Gram-Negative Pathogens Recovered from Patients Enrolled in the Phase 2 Trials for Ceftazidime-Avibactam: Clinical Efficacies Analyzed against Subsets of Molecularly Characterized Isolates

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The correlation of the clinical efficacies of ceftazidime-avibactam and comparators (carbapenems) was evaluated against baseline Gram-negative isolates having characterized β-lactam resistance mechanisms from complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) phase 2 trials. *Enterobacteriaceae* displaying ceftriaxone and/or ceftazidime MICs of ≥2 μg/ml (69 isolates) and nonfermentative Gram-negative bacilli (NF-GNB [three isolates]) with ceftazidime MICs of ≥16 μg/ml were characterized for their narrow- and extended-spectrum β-lactamase (ESBL) content. *Enterobacteriaceae* (one isolate) and NF-GNB (three isolates) with imipenem/meropenem MICs of ≥2 and ≥16 μg/ml, respectively, were tested for carbapenemases. All cUTI *E. coli* had the lineage background investigated (ST131-like versus non-ST131-like). The primary efficacy endpoint was microbiological response (eradication) at test of cure (TOC) for cUTI and clinical response (inferred microbiological eradication) at TOC for cIAI. A total of 34.1% of baseline cUTI (36.4%) and cIAI (33.1%) pathogens met the MIC-based screening criteria (screen positive). All screen-positive cUTI pathogens were CTX-M-producing *E. coli*, except for one *E. cloacae* isolate with AmpC overexpression. The majority (66.7%) of screen-positive cIAI isolates produced CTX-M-type coupled with a diverse array of other β-lactamases. Similar favorable responses were observed with ceftazidime-avibactam (93.3%) and carbapenems (90.9%), when a non-ESBL *Enterobacteriaceae* isolate was recovered at the baseline visit. When an ESBL *Enterobacteriaceae* isolate was present, the favorable responses were 85.7% and 80.0% with ceftazidime-avibactam and carbapenems, respectively. Higher favorable responses were observed with ceftazidime-avibactam (75.0%) than with carbapenems (66.7%) when an ST131-like *E. coli* isolate was recovered at baseline, as when a non-ST131-like isolate was present (93.8% versus 86.7%, respectively). The efficacy of ceftazidime-avibactam was similar to that of carbapenems for treatment of cUTI and cIAI caused by ESBL organisms.

Enterobacteriaceae are a common cause of community-acquired and health care-acquired infections, with *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp. among the most common organisms (1). Antimicrobial resistance among *Enterobacteriaceae* mostly reflects the worldwide emergence and dissemination in the late 1980s of extended-spectrum β-lactamases (ESBLs), such as bla_{TEM} and bla_{SHV} allelic variants (1). However, the epidemiology of these isolates changed dramatically during early years of 2000s, and TEM and SHV ESBL-encoding genes have slowly been replaced by bla_{CTX-M} genes, which have been detected in community- and hospital-acquired *Enterobacteriaceae* (2–4). In 2012, 10.1% (581/5,739) of *E. coli*, *Klebsiella*, and *Proteus mirabilis* isolates from U.S. hospitals were found to carry ESBL genes, and the majority (61.6%) of those were bla_{CTX-M} (5).

During the late 1990s, carbapenem-resistant *Enterobacteriaceae* (CRE) began to emerge (6). In 2012, 4.6% of acute care hospitals reported at least one CRE isolate, and the proportion of *Enterobacteriaceae* that were CRE increased from 1.2% in 2001 to 4.2% in 2011 in the National Nosocomial Infection Surveillance system (NNIS) and the National Healthcare Safety Network (NHSN) and from 0% in 2001 to 1.4% in 2010 in the Surveillance Network–USA (TSN) (1). Overall, the majority of CRE isolates in the United States harbor a *Klebsiella pneumoniae* carbapenemase (KPC) serine carbapenemase-encoding gene (6). bla_{KPC} genes are mostly detected in *Klebsiella pneumoniae*, but they have been observed in numerous *Enterobacteriaceae* species and have become endemic in several hospitals worldwide (7).

CRE isolates often demonstrate a susceptible phenotype to polymyxin B compounds and tigecycline only (8) and correlate significantly to the patients' degree of morbidity (9). Thus, the use of broad-spectrum β-lactamase inhibitor compounds in combination with β-lactam agents is a promising option in development for treatment of infections caused by ESBL and carbapenemase producers (10). Avibactam is a novel non-β-lactam β-lactamase inhibitor of β-lactam-hydrolyzing enzymes belonging to Ambler structural classes A and C, as well as some class D enzymes (10). Previous phase 2 clinical trials demonstrated the efficacy, safety,

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and tolerability of ceftazidime-avibactam versus comparator agents for treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) (11, 12). The present study characterized the β-lactamase genes in baseline pathogens recovered during those phase 2 trials. In addition, this study correlates the efficacy of ceftazidime-avibactam and comparators against subsets of isolates harboring β-lactam resistance mechanisms.

MATERIALS AND METHODS

Patients, clinical isolates, study treatment, and endpoints. Male and female patients between the ages of 18 and 90 years were enrolled in the phase 2 clinical trials for ceftazidime-avibactam (clinicaltrials.gov identifiers NCT00752219 and NCT00690378) (11, 12). Hospitalized patients were enrolled from medical centers located in Guatemala, India, Jordan, Lebanon, and the United States for the cUTI trial and Bulgaria, France, India, Lebanon, Poland, Romania, Russia, and the United States for the cIAI trial.

Patients eligible for the cUTI trial were stratified by diagnosis (acute pyelonephritis or other cUTI) and randomized 1:1 to 0.5 g ceftazidime–0.125 g avibactam (here, "0.5/0.125 g") (intravenous [i.v.] every 8 h) or imipenem-cilastatin (0.5 g i.v. every 6 h). Oral ciprofloxacin (0.5 g twice daily) or alternative oral therapy was permitted after at least 4 days of initial i.v. therapy. Pathogens were recovered via urine culture at the baseline (the first one being termed "baseline") and follow-up visits. Blood cultures were performed when clinically indicated or in patients with indwelling catheters and stents. The primary efficacy endpoint was microbiological response at test of cure (TOC), 5 to 9 days after end of treatment in the microbiologically evaluable (ME) population. Clinical response was a secondary endpoint.

For cIAI, eligible patients with a presumed (preoperative) or definitive (intraoperative or postoperative) diagnosis of cIAI were randomized 1:1 to ceftazidime-avibactam (2/0.5 g i.v. every 8 h) and metronidazole (0.5 g i.v. every 8 h) or meropenem (1 g i.v. every 8 h) plus placebo. Isolates were obtained during the study qualifying operative procedure (i.e., laparotomy, laparoscopy, or percutaneous drainage) and during any subsequent operative procedures. Blood cultures were also collected from all patients at the baseline visit. The primary efficacy endpoint was clinical response at TOC, 2 weeks after the end of treatment in the ME population. The ME population was defined as clinically evaluable patients with a confirmed cUTI or cIAI, at least one baseline pathogen susceptible to the study therapy agents, who received treatment, and who had a clinical assessment at the TOC visit (see references 11 and 12 for additional information).

For the cUTI trial, a favorable response was defined as eradication of all pathogens from urine ($<10^4$ CFU/ml) and blood, while in the cIAI trial, a favorable response was defined as complete resolution or significant improvement of signs/symptoms of infection with no requirements for additional antimicrobial therapy (11, 12).

Selection criteria for β-lactamase screen and analysis. All baseline isolates were centrally tested for susceptibility by broth microdilution (Clinical and Laboratory Standards Institute [CLSI] standard M07-A9, 2012) (13). *Enterobacteriaceae* displaying ceftriaxone and/or ceftazidime MIC results of ≥2 μg/ml and nonfermentative Gram-negative bacilli (NF-GNB) with ceftazidime MIC results of ≥16 μg/ml were selected for further characterization of narrow- and extended-spectrum β-lactamase (ESBL) genes. *Enterobacteriaceae* and NF-GNB isolates exhibiting imipenem/meropenem MIC results of ≥2 and ≥16 μg/ml, respectively, were tested for the presence of carbapenemase-encoding genes, as previously described (14–17).

Isolates that met the MIC screening criteria described above were subjected to a microarray-based assay, the Check-MDR CT101 kit, according to the manufacturer's instructions (Check-Points, Wageningen, Netherlands). This kit has the capabilities to detect CTX-M groups 1, 2, 8 + 25, and 9, non-ESBL and ESBL variants of TEM and SHV, plasmid AmpC (ACC, ACT/MIR, CMY, DHA, and FOX), and KPC- and NDM-encoding genes (14). Supplemental multiplex PCR assays were utilized to detect additional ESBL-encoding genes (bla_{GES}, bla_{VEB}, bla_{PER}, and oxacillinase enzyme genes [bla_{OXA-2}, bla_{OXA-10}, and bla_{OXA-13} groups, bla_{OXA-18}, and bla_{OXA-45}]) (14) and carbapenemase-encoding genes (bla_{IMP}, bla_{VIM}, bla_{NDM-1}, bla_{OXA-48}, bla_{GES}, bla_{NMC-A}, bla_{SME}, and bla_{IMI}) (15). *Acinetobacter* species isolates were also screened for the bla_{OXA-23}, bla_{OXA-24}, and bla_{OXA-58} groups (16). All results obtained by the Check-Points and supplemental PCR assays were confirmed by single PCRs and subsequent determination of the gene allele by sequencing analysis of both strands (Sanger method); nucleotide and amino acid sequences were analyzed using the Lasergene software package (DNASTAR, Madison, WI). Amino acid sequences were compared with those available through the internet using BLAST (http://www.ncbi.nlm.nih.gov/blast/).

The transcription levels of the chromosomally encoded AmpC were determined in *Pseudomonas aeruginosa*, *E. coli*, and *Enterobacter cloacae*. The transcription levels of the chromosomal *ampC* gene were determined by the quantification of the target gene mRNA using a normalized expression analysis method and relative comparison to susceptible control strains (18, 19). A given strain was considered to overexpress the *ampC* gene when at least a 10-fold greater difference of *ampC* transcripts was detected compared with a species-specific wild-type reference control strain.

Determination of *E. coli* strains associated with ST131 and PFGE. All *E. coli* strains recovered during the cUTI trial were investigated by pulsed-field gel electrophoresis (PFGE) for the presence of two single nucleotide polymorphisms (SNPs), namely, thymine 144 and adenine 450 in the *pabB* gene, as previously described by Dhanji et al. (20). The presence of these two SNPs is known to be unique to sequence type 131 (ST131) strains, and they were described here as "ST131-like."

RESULTS

Study population. A total of 192 ME patients were included in the study, with 26 and 20 ME patients included in the ceftazidime-avibactam and carbapenem arms, respectively, for the cUTI trial, while 60 and 70 patients, respectively, were included in the arms for the cIAI trial (11, 12). Most ME patients had a single baseline aerobic Gram-negative pathogen recovered during the screening visit, except for four (4/62 [6.5%]) patients in the cUTI trial and 14 (14/130 [10.8%]) patients in the cIAI trial who had multiple aerobic Gram-negative organisms recovered at the baseline visit (see Tables 2 and 3).

Antimicrobial susceptibility profiles. Table 1 lists the MIC values obtained for baseline isolates recovered from ME patients enrolled in both the cIAI and cUTI trials. Baseline *Enterobacteriaceae* isolates recovered from cIAI demonstrated a bimodal MIC distribution when tested against ceftazidime, with one modal MIC of 0.12 μg/ml and a second mode at >32 μg/ml. Avibactam restored the ceftazidime activity, including against ESBL-positive isolates, with a modal MIC value of 0.06 μg/ml (the highest MIC of 2 μg/ml). One exception was observed against a carbapenemase (NDM-1)-producing *K. pneumoniae* strain exhibiting ceftazidime-avibactam MIC results of >32 μg/ml. All baseline NF-GNB from the cIAI trial showed ceftazidime-avibactam MICs at ≤8 μg/ml, except for one *P. aeruginosa* isolate (32 μg/ml) expressing VIM-2 and two *A. baumannii* strains producing PER-1 (32 μg/ml) or OXA-23 (>32 μg/ml). Against baseline *Enterobacteriaceae* from cUTI patients, ceftazidime alone showed a bimodal MIC distribution and inhibited 68.3% of tested isolates at the breakpoint for susceptibility (i.e., ≤4 μg/ml). Ceftazidime-avibactam and imipenem had the same modal MIC value (0.12 μg/ml) against *Enterobacteriaceae* isolates causing cUTI.

β-Lactamase profiles. Totals of 38.7% (24/62) and 35.4% (46/

TABLE 1 MIC results for ceftazidime, ceftazidime-avibactam, and imipenem or meropenem obtained against baseline aerobic Gram-negative pathogens recovered from the ME population

Trial	Organism	Agent[a]	No. of isolates at MIC (μg/ml) of:											
			≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
cIAI	*Enterobacteriaceae*[b]	CAZ		16	42	24	2	1	1	1		6	13	24
		CAZ-AVI	19	52	36	11	4	3	4					1[c]
		MER	127	1		1				1[c]				
	Pseudomonas spp.[d]	CAZ			1				6	1	2		1[e]	
		CAZ-AVI			1			1	6	1	1		1[e]	
		MER	1	2	2	2			2	1		1[e]		
	Acinetobacter spp.[f]	CAZ						1	1					2[g]
		CAZ-AVI					1			1			1[g]	1[g]
		MER	1		1									2[g]
cUTI	*Enterobacteriaceae*[h]	CAZ	2	4	22	6	3	3	3		2	5	5	8
		CAZ-AVI	8	17	28	9			1					
		IMI		17	40	6								
	P. aeruginosa	CAZ							3					
		CAZ-AVI							3					
		IMI					1	2						

[a] CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; MER, meropenem; IMI, imipenem.
[b] Includes 103 *E. coli* isolates, 16 *K. pneumoniae* isolates, four *K. oxytoca* isolates, three *E. cloacae* isolates, and one isolate each of *Citrobacter freundii*, *Citrobacter braakii*, *Enterobacter aerogenes*, and *P. mirabilis*.
[c] One NDM-1-producing *K. pneumoniae* isolate.
[d] Includes eight *P. aeruginosa* isolates, two *P. fluorescens* isolates, and one *P. stutzeri* isolate.
[e] Includes one VIM-2-producing *P. aeruginosa* isolate.
[f] Includes three *A. baumannii* isolates and one *A. junii* isolate.
[g] Includes one PER-1-producing *A. baumannii* isolate and one OXA-23-producing *A. baumannii* isolate.
[h] Includes 59 *E. coli* isolates, two *P. mirabilis* isolates, and one isolate each of *Citrobacter koseri* and *E. cloacae*.

130) of the ME patients in the cUTI and cIAI trials, respectively, had baseline pathogens that met the MIC screening criteria (i.e., were screen positive) (Tables 2 and 3). *E. coli* alone comprised the vast majority (88.7%) of the causative pathogens responsible for cUTI, and 38.2% met the MIC screening criteria. These isolates produced CTX-M-14 (9.5%) or CTX-M-15 (90.5%), and almost half (42.1%) of the CTX-M-15 *E. coli* producers also carried $bla_{\text{OXA-1/30}}$. In addition, hyperproduction of the intrinsic chromosomally encoded AmpC enzyme was detected in one CTX-M-15 *E. coli* isolate. Except for one *E. cloacae* strain hyperproducing AmpC, other baseline cUTI pathogens did not meet the screening criteria (i.e., were screen negative).

Among aerobic Gram-negative bacteria, *E. coli* alone represented the vast majority of baseline cIAI pathogens (70.0%), and approximately one-third (36.3%) of those isolates met the MIC screening criteria. Among these, 75.8% (25/33) carried $bla_{\text{CTX-M-15}}$ alone or in combination with bla_{SHV} and/or $bla_{\text{OXA-1/30}}$ and/or plasmid AmpC genes (i.e., bla_{ACC} and bla_{CMY} variants). Other *E. coli* isolates carried $bla_{\text{OXA-1/30}}$ and/or bla_{SHV} and/or bla_{CMY} enzymes. Among *K. pneumoniae* isolates, 50.0% met the MIC screening criteria, and $bla_{\text{CTX-M-15}}$, either alone or with $bla_{\text{OXA-1/30}}$ and/or $bla_{\text{SHV-5}}$, was present in 50.0% (3/6) of investigated bacteria. One *K. pneumoniae* isolate carried $bla_{\text{NDM-1}}$ and $bla_{\text{CTX-M-15}}$. NF-GNB (three *P. aeruginosa* isolates) recovered from cUTI patients were screen negative (Table 2), while three out of 15 cIAI NF-GNB met the MIC screening criteria. These three isolates were two *A. baumannii* isolates—one producing OXA-23 and the

TABLE 2 Summary of baseline aerobic Gram-negative pathogens recovered from each patient in the ME population in the cUTI trials for ceftazidime-avibactam[a]

Pathogen(s) in each patient (no. of patients)	Result (no. [%] of isolates)[b]
E. coli (55)	Screen negative (34 [61.8]) Screen positive (21 [38.2]) CTX-M-14 (2) CTX-M-15[c] (11) CTX-M-15 + OXA-1/30 (8)
E. cloacae (1)	AmpC overexpression (1)
E. coli-C. koseri (1)	Screen negative for *E. coli* (1) and *C. koseri* (1)
E. coli-P. mirabilis (1)	CTX-M-15 for *E. coli* (1) and screen negative for *P. mirabilis* (1)
P. mirabilis (1)	Screen negative (1)
P. aeruginosa (1)	Screen negative (1)
P. aeruginosa-E. coli (2)	Screen negative for *P. aeruginosa* (1) and *E. coli* (1) Screen negative for *P. aeruginosa* (1) and CTX-M-15 + OXA-1/30 for *E. coli* (1)

[a] The cUTI trial results shown represent 62 ME patients.
[b] Screen negative, isolates that did not meet the MIC-based screening criteria; screen positive, isolates that met the screening criteria (i.e., ceftriaxone and/or ceftazidime MICs of ≥2 μg/ml, NF-GNB with ceftazidime MICs of ≥16 μg/ml, and *Enterobacteriaceae* and NF-GNB isolates exhibiting imipenem and meropenem MICs of ≥2 and ≥16 μg/ml, respectively). All *Enterobacteriaceae* and NF-GNB isolates had imipenem MICs of ≤0.25 and ≤2 μg/ml, respectively.
[c] Hyperproduction of the intrinsic AmpC enzyme was detected in one $bla_{\text{CTX-M-15}}$-carrying isolate.

TABLE 3 Summary of baseline aerobic Gram-negative pathogens recovered from patients in the ME population in the cIAI trials for ceftazidime-avibactam[a]

Pathogen(s) in each patient (no. of patients)	Result (no. of isolates [% within species])[b]
E. coli (91)	Screen negative (58 [63.7]) Screen positive (33 [36.3]) CTX-M-15 (4) CTX-M-15 + SHV-12 (1) CTX-M-15 + OXA-1/30 + ACC-4 (1) CTX-M-15 + OXA-1/30 (14) CTX-M-15 + OXA-1/30 + CMY-42 (3) CTX-M-15 + OXA-1/30 + SHV-12 (1) CTX-M-15 + OXA-1/30 + SHV-2 (1) OXA-1/30 (1) SHV-12 (3) CMY-6 (1) CMY-42 (2) OXA-1/30 + CMY-42 (1)
K. pneumoniae (12)	Screen negative (6 [60.0]) Screen positive (6 [40.0]) CTX-M-15 (1) CTX-M-15 + OXA-1/30 (1) CTX-M-15 + OXA-1/30 + SHV-5 (1) NDM-1 + CTX-M-15 (1) Other screen positive[c] (2)
C. braakii (1)	CTX-M-15 (1)
C. freundii (1)	Screen negative (1)
E. cloacae (3)	Screen negative (2) Screen positive (1)
E. aerogenes (1)	Screen negative (1)
K. oxytoca (2)	Screen negative (2)
P. mirabilis (1)	ACC-4 (1)
E. coli-K. pneumoniae (3)	Screen negative for *E. coli* (2) and *K. pneumoniae* (2) CTX-M-15 + OXA1/30 + SHV-31 for *E. coli* (1) and CTX-M-15 for *K. pneumoniae* (1)
E. coli-K. oxytoca (2)	Screen negative for *E. coli* (2) and *K. oxytoca* (2)
E. coli-A. baumannii (1)	CTX-M-15 for *E. coli* (1) and OXA-23 for *A. baumannii* (1)
P. aeruginosa (2)	Screen negative (1) VIM-2 + OXA-4 + OXA-10 (1)
P. aeruginosa-E. coli (4)	Screen negative for *P. aeruginosa* (4) and *E. coli* (4)
P. aeruginosa-A. junii (1)	Screen negative for *P. aeruginosa* (1) and *A. junii* (1)
P. aeruginosa-A. baumannii (1)	Screen negative for *P. aeruginosa* (1) and PER-1 for *A. baumannii* (1)
A. baumannii (1)	Screen negative (1)
P. fluorescens (1)	Screen negative (1)
P. fluorescens-E. coli-K. pneumoniae (1)	Screen negative for *P. fluorescens* (1), *E. coli* (1), and *K. pneumoniae* (1)
P. stutzeri-E. coli (1)	Screen negative for *P. stutzeri* (1) and *E. coli* (1)

[a] The cIAI results shown represent 130 ME patients.
[b] Screen negative, isolates that did not meet the MIC-based screening criteria; screen positive, isolates that met the screening criteria (i.e., ceftriaxone and/or ceftazidime MICs of ≥2 μg/ml, NF-GNB with ceftazidime MICs of ≥16 μg/ml, and *Enterobacteriaceae* and NF-GNB isolates exhibiting imipenem and meropenem MICs of ≥2 and ≥16 μg/ml, respectively). CMY-42 is a single-amino-acid-change (V231S) variant of CMY-2.
[c] Some isolates met the phenotypic MIC screening criteria, but targeted β-lactamase resistance mechanisms were not detected.

other PER-1—and one VIM-2-producing *P. aeruginosa* isolate (Table 3).

Efficacy analysis of ceftazidime-avibactam and carbapenems in the ME population. Table 4 summarizes the favorable response at the TOC assessment among the ME patients enrolled in the cUTI and cIAI phase 2 trials for ceftazidime-avibactam. Organisms associated with clinical or microbiological failure are presented in Table 5. Overall, favorable responses at the TOC visit were observed in 93.3 and 90.9% of ceftazidime-avibactam and comparator patients, respectively, for both trials combined when baseline MIC-based screen-negative *Enterobacteriaceae* isolates were recovered and in 85.7 and 80.0% of patients, respectively, when an ESBL-producing *Enterobacteriaceae* isolate was recovered at baseline. Favorable outcome was noted in 84.6% (22/26) of patients in the ceftazidime-avibactam arm when CTX-M-15 (alone or with additional enzymes)-producing *Enterobacteriaceae* was recovered at the baseline visit and in 79.2% (19/24) of patients in the carbapenem arms. In neither the ceftazidime-avibactam nor carbapenem arms of either of the trials could the microbiological or clinical failures be ascribed to high MIC of the antibacterial agent or possession of particular β-lactamase genes (Table 5).

Similar proportions of patients with favorable outcomes were observed for the ceftazidime-avibactam and carbapenem arms in the phase 2 cIAI trial, regardless of the presence of MIC-based screen-positive or -negative *Enterobacteriaceae* recovered at baseline (91.7 and 90.3% for ceftazidime-avibactam and 94.4 and 90.9% for carbapenem, respectively). Favorable outcome in the ceftazidime-avibactam arm of the phase 2 cUTI trial was less frequent (72.7%) when an isolate that met the MIC screening criteria was recovered at baseline than for patients with MIC-based screen-negative isolates (93.8%). The favorable outcome rate (61.5%) in the imipenem cUTI arm when MIC-based screen-positive *Enterobacteriaceae* were identified at baseline was lower than that (90.9%) for patients with a screen-negative isolate.

Overall, for both trials combined, favorable responses were documented for 85.7% (6/7) and 100.0% (9/9) of patients in the ceftazidime-avibactam and carbapenem arms, respectively, when an NF-GNB isolate was identified at baseline. In addition, favorable response rates of 75.0% (6/8) and 66.7% (2/3) were noted at the TOC for patients in the ceftazidime-avibactam and imipenem arms, respectively, of the cUTI trial, when ST131-like *E. coli* isolates were identified at baseline. These rates were 93.8% (15/16) and 86.7% (26/30) for the ceftazidime-avibactam and imipenem arms, respectively, when non-ST131-like *E. coli* isolates were recovered at baseline. Of note, three cIAI patients from the meropenem arm had carbapenemase-producing isolates. These isolates were one OXA-23 *A. baumannii* isolate (meropenem MIC, 16 μg/ml), one VIM-2 *P. aeruginosa* isolate (meropenem MIC, >16 μg/ml), and one NDM-1 *K. pneumoniae* isolate (meropenem MIC, 4 μg/ml) (Table 3). In addition, the patient infected with OXA-23-producing *A. baumannii* also had a CTX-M-15 *E. coli* isolate. All three patients had a favorable outcome.

DISCUSSION

Overall, 35.2% (38.1 and 33.8% of cUTI and cIAI isolates, respectively) of all baseline *Enterobacteriaceae* met the MIC-based-screening criteria at the baseline visit. Previous studies have reported rates of ESBL isolates of 3.7 and 2.4% for cUTI and cIAI, respectively, in large phase 3 clinical trials (21) or 16.2% in community-acquired cIAI (22). Recent phase 3 clinical trials for cef-

TABLE 4 Summary of favorable responses at the TOC assessment among the ME patients enrolled in the cUTI and cIAI phase 2 trials for ceftazidime-avibactam

Trial	Organism(s)	Category[a]	Result for treatment arm by no. of patients with favorable response/total (%)[b]	
			Ceftazidime-avibactam	Carbapenem
cIAI and cUTI combined	*Enterobacteriaceae*[c]	Screen negative	42/45[d] (93.3)	60/66 (90.9)
		Screen positive	30/35 (85.7)	24/30[e] (80.0)
		CTX-M-15	22/26 (84.6)	19/24 (79.2)
		CTX-M-15 alone	8/8 (100.0)	6/10 (60.0)
		CTX-M-15 + additional ESBLs	14/18 (77.8)	17/19 (89.5)
		Other enzymes	8/9 (88.9)	5/6 (83.3)
	NF-GNB[f]	All	6/7[g] (85.7)	9/9[h] (100.0)
cIAI	*Enterobacteriaceae*	Screen negative	28/31 (90.3)	40/44[i] (90.9)
		Screen positive	22/24 (91.7)	17/18[i] (94.4)
cUTI	All[j]	Screen negative	15/16[k] (93.8)	20/22[l] (90.9)
		Screen positive	8/11 (72.7)	8/13 (61.5)
	E. coli	ST131	6/8 (75.0)	2/3 (66.7)
		Non-ST131	15/16 (93.8)	26/30 (86.7)

[a] Screen negative, isolates that did not meet the MIC-based screening criteria; screen positive, isolates that met the screening criteria (i.e., ceftriaxone and/or ceftazidime MICs of ≥2 μg/ml and NF-GNB with ceftazidime MICs of ≥16 μg/ml, and *Enterobacteriaceae* and NF-GNB isolates exhibiting imipenem and meropenem MICs of ≥2 and ≥16 μg/ml, respectively).
[b] Results are expressed as the number of patients with favorable responses/total number of patients in each category (percentage) and represent the ceftazidime-avibactam or imipenem-cilastatin arms for cUTI and the ceftazidime-avibactam plus metronidazole or meropenem arms for cIAI.
[c] Patients from whom *Enterobacteriaceae* pathogens were recovered at the baseline visit.
[d] Includes one patient with a polymicrobial infection caused by *E. coli* and *C. koseri* at the baseline visit.
[e] Includes one patient with a polymicrobial infection caused by aerobic Gram-negative pathogens (*E. coli* and *K. pneumoniae*).
[f] Patients infected with NF-GNB pathogens with or without concomitant culture of aerobic *Enterobacteriaceae* isolates at the baseline visit.
[g] Includes six patients with polymicrobial infections (4 with *P. aeruginosa-E. coli*, 1 with *P. aeruginosa-A. baumannii*, and 1 with *P. stutzeri-E. coli*).
[h] Includes five patients with polymicrobial infections (2 with *P. aeruginosa-E. coli*, 1 with *E. coli-A. baumannii*, and 1 with *P. fluorescens-E. coli-K. pneumoniae*).
[i] Includes one patient with a polymicrobial infection (*E. coli-K. pneumoniae*) with β-lactamase-producing pathogens and four patients with polymicrobial infections (2 with *E. coli-K. pneumoniae* and 2 with *E. coli-K. oxytoca*) with MIC-based screen-negative pathogens.
[j] Patients infected with *Enterobacteriaceae* pathogens, unless otherwise indicated.
[k] Includes two patients with polymicrobial infection (1 with *E. coli-P. aeruginosa* and 1 with *E. coli-C. koseri*) and one patient infected with a *P. aeruginosa* isolate at baseline.
[l] Includes two patients with polymicrobial infections (1 with *E. coli-P. aeruginosa* and 1 with *E. coli-P. mirabilis*) at baseline.

tolozane-tazobactam reported ESBL rates in *Enterobacteriaceae* of 14.8 and 7.2% for cUTI and cIAI, respectively (23, 24). These rates can be influenced by geography, population, and enrollment criteria, among other factors. However, the ESBL rates reported here seem to be higher than most rates documented previously. In addition, *E. coli* comprised the most common pathogen in both trials, consistent with previous results (23–26), and ESBL rates among this pathogen were 36.3% among baseline *E. coli* isolates causing cIAI and 38.2% in those causing cUTI. However, other smaller studies have reported ESBL rates of up to 60% in *E. coli* isolates causing cUTI (18, 27).

Among the MIC-based screen-positive *Enterobacteriaceae* presented here, production of CTX-M-type enzymes, with or without the presence of OXA-1/30, was the most prevalent β-lactam resistance mechanism. Recent publications have reported the increased prevalence of CTX-M-type enzymes in *Enterobacteriaceae*, especially *E. coli*, regardless of infection source (i.e., hospital versus community acquired) (14, 15, 28). Interestingly, compared with the baseline *Enterobacteriaceae* isolates causing cUTI, those responsible for cIAI demonstrated a more heterogeneous β-lactamase genetic profiling. The reasons for these differences are unclear but might perhaps be attributed to geographical differences or other patient differences between trial populations.

Overall, the rate of favorable responses was 90 to 93% for both arms (ceftazidime-avibactam and carbapenems) in the aggregated data analysis (both trials combined) when an *Enterobacteriaceae* isolate that did not meet the screening criteria was cultured at the baseline visit. The rate of favorable responses decreased when infections were caused by isolates that met the MIC screening criteria (screen-positive isolates), with a rate for ceftazidime-avibactam (85.7%) slightly higher than that obtained for the carbapenems (80.0%). The latter overall rates were driven by those responses obtained from the cUTI trial, where the presence of a screen-positive isolate at the baseline visit predicted a less favorable outcome (72.7 and 61.5% for ceftazidime-avibactam and imipenem, respectively) compared to when a screen-negative isolate was recovered (93.8 and 90.9% for ceftazidime-avibactam and imipenem, respectively). The reasons for these findings are uncertain, although they may be related to underlying patient factors associated with acquisition of drug-resistant bacteria. The phase 2 trials were not powered to demonstrate noninferiority,

TABLE 5 Summary of results from patients with unfavorable response at the TOC assessment among the ME patients enrolled in the cUTI and cIAI phase 2 trials for ceftazidime-avibactam

Trial[a]	Arm[b]	Patient no.	Age (yr)	Pathogen	MIC (μg/ml)			Molecular characterization
					CAZ	CAZ-AVI	MER/IMI	
cUTI	CAZ-AVI	1	28	*E. coli*	1	0.12	0.12	CTX-M-14 + TEM-1
		2	36	*E. coli*	>32	0.25	0.12	CTX-M-15 + OXA-1 + TEM-1
		3	57	*E. coli*	8	0.12	0.12	CTX-M-15 + OXA-1
		4	36	*P. aeruginosa*	4	4	0.5	Screen negative[c]
	IMI	5	76	*E. coli*	32	0.12	0.06	CTX-M-15 + TEM-1
		6	34	*E. coli*	>32	0.12	0.12	CTX-M-15 + TEM-1
		7	45	*E. coli*	8	0.12	0.12	CTX-M-15 + TEM-1
		8	45	*E. coli*	0.5	0.12	0.12	Screen negative
		9	50	*E. coli*	16	0.12	0.12	CTX-M-15 + TEM-1
				P. mirabilis	≤0.03	≤0.03	0.25	Screen negative
		10	68	*E. coli*	0.12	0.06	0.12	Screen negative
		11	71	*E. cloacae*	>32	2	0.25	Upregulated AmpC + TEM-1
cIAI	CAZ-AVI/MTZ	1	52	*E. coli*	16	≤0.03	≤0.004	CTX-M-15 + OXA-1 + SHV-2
		2	40	*E. coli*	>32	2	0.015	CTX-M-15 + OXA-1 + CMY-42
		3	49	*E. coli*	0.25	0.12	0.015	Screen negative
		4	30	*E. coli*	0.06	≤0.03	0.008	Screen negative
		5	33	*E. coli*	0.12	0.12	0.015	Screen negative
	MER	6	20	*E. coli*	>32	0.12	0.015	CTX-M-15 + OXA-1 + SHV-12 + TEM-1
		7	82	*E. aerogenes*	0.12	0.12	0.03	Screen negative
		8	39	*E. coli*	0.12	0.06	0.015	Screen negative
		9	69	*E. coli*	0.12	0.06	0.015	Screen negative
		10	26	*E. coli*	0.12	0.06	0.015	Screen negative

[a] cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection.
[b] CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; MER, meropenem; IMI, imipenem.
[c] Screen negative, isolates that did not meet the MIC-based screening criteria.
[d] Patient with polymicrobial infections (*E. coli*-*P. mirabilis*) at baseline. A molecularly unrelated (PFGE) *E. coli* isolate (CTX-M-15 + OXA-1) was recovered at visit 5.
[e] A CTX-M-15-producing *E. coli* isolate was recovered at visit 5.
[f] A molecularly unrelated (by PFGE) *E. coli* isolate (NDM-1 + CTX-M-15 + OXA-1 + CMY-2) was recovered at the follow-up visit.

and additional studies with larger numbers of patients are needed to further evaluate and confirm these results.

In this study, the number of ST131 isolates causing cUTI was relatively small (19.3% versus 80.7% for non-ST131 strains). The prevalence of ST131 among *E. coli* isolates varies among studies, mostly due to different organism inclusion criteria (29), and rates of ST131 isolates causing UTI of 12% have been reported in one study (30), while another study documented a rate of 30% of *E. coli* isolates causing pyelonephritis in Australia (31). The rates of a favorable cUTI outcome due to ST131 strains reported here were 75.0 and 66.7% for ceftazidime-avibactam and imipenem-cilastatin, respectively, while higher rates were documented when non-ST131 strains were recovered at the baseline visit (93.8 and 86.7%, respectively). These results indicate a higher treatment failure for patients infected with ST131, which corroborates a recent report published by Can et al. (31). *E. coli* ST131 is a multidrug-resistant (MDR) clonal group that has spread throughout the world (32). Overall, clonal expansion of ST131 is the predominant mechanism for the rising prevalence of both fluoroquinolone resistance and CTX-M-15 producers among *E. coli*, and consequently the ST131 *E. coli* population causing infections in humans (33). The dissemination of MDR strains of *E. coli* has challenged the empirical treatment, especially UTI, and increased morbidity and mortality (34). However, a few studies have reported similar mortality rates between infections caused by ST131 and non-ST131 strains (35, 36).

The results presented here document high rates of MIC-based screen-positive pathogens causing cUTI and cIAI, which support the current recommendations for empirical treatment of such infections (carbapenems for both cUTI and cIAI). These clinical trial results suggest that the efficacy of ceftazidime-avibactam (with metronidazole for cIAI) may be similar to that of imipenem for the treatment of cUTI or meropenem for the treatment of cIAI caused by ESBL producers, including prevalent CTX-M-15 *Enterobacteriaceae*.

Limitations of this study include the relatively small number of ME patients available for analysis in each arm of each trial and the even smaller numbers of patients infected by ESBL organisms. Therefore, trial results were also analyzed in aggregate to increase the number of patients for a more robust data analysis. Therefore, it is also important to mention that the patients originated from two different trial designs with distinct primary efficacy endpoints. Similarly, the association of specific *E. coli* lineages (ST131) with outcomes may be limited as a consequence of the small number sampled. In addition, this study evaluated aerobic Gram-negative pathogens only and did not take into consideration the presence of polymicrobial infections caused by Gram-positive bacteria and/or anaerobes, especially in the cIAI arms.

Moreover, the isolates investigated here may possess β-lactam resistance mechanisms other than those screened in this study, such as other β-lactamases and/or decreased permeability.

In summary, this study shows high proportions (36.4 and 33.1% in the cUTI and cIAI trials, respectively) of aerobic Gram-negative isolates that met the screening criteria for ESBL production. All but one baseline pathogen from the cUTI trial that met the MIC screening criteria produced CTX-M enzymes, showing the dominance of CTX-M isolates causing cUTI. In contrast, a greater diversity of ESBL-encoding genes was observed among baseline isolates causing cIAI. Moreover, the efficacy of ceftazidime-avibactam was similar to that of carbapenems for treatment of cUTI and cIAI caused by ESBL organisms. However, these phase 2 clinical trials were not powered to demonstrate noninferiority, and 95% confidence intervals for the differences in responses between ceftazidime-avibactam and carbapenem treatments were expectedly wide (11, 12). Likewise, although favorable responses were similar between ceftazidime-avibactam and carbapenem for the subgroups presented here, formal statistical comparisons were not performed due to the small sample sizes and consequent large 95% confidence intervals for the treatment differences. Further and more robust analyses with a larger sample size are necessary to confirm these results, which can be expected when the phase 3 trials' results for ceftazidime-avibactam become available.

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