Table 1. Baseline Characteristics of the Study Groups

	cUTI		cIAI	
	CAZ-AVI (n = 144)	BAT (n = 137)	CAZ-AVI + MET (n = 10)	BAT (n = 11)
Age, y	64.3 ± 14.6	61.3 ± 15.3	49.9 ± 16.1	68.4 ± 11.1
Female	64 (44.4)	63 (46.0)	6 (60.0)	4 (36.4)
Race				
White	136 (94.4)	131 (95.6)	9 (90.0)	11 (100)
Other[a]	8 (5.6)	6 (4.4)	1 (10.0)	0
BMI, kg/m^2	28.1 ± 5.5	28.0 ± 5.8	25.2 ± 6.3	28.6 ± 4.6
Renal status[b]				
> 50	118 (81.9)	113 (82.5)	10 (100)	6 (54.5)
31-50	19 (13.2)	18 (13.1)	0	3 (27.3)
16-30	4 (2.8)	5 (3.6)	0	2 (18.2)
6-15	3 (2.1)	1 (0.7)	0	0

Data presented in mean ± SD or No. (%).

BAT, best available therapy; BMI, body mass index; CAZ-AVI, ceftazidime-avibactam; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; MET, metronidazole.

[a]Black or African American, Asian, or other.

[b]Creatinine clearance, mL/min.

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The majority of patients were infected with Enterobacteriaceae, most commonly *Escherichia coli* and *Klebsiella pneumoniae*. The overall clinical cure rate (cUTI and cIAI) at TOC in the mMITT population was 140 of 154 (90.9%; 95% CI, 85.6% to 94.7%) for CAZ-AVI and 135 of 148 (91.2%; 95% CI, 85.9% to 95.0%) for BAT. For patients with cUTI, the clinical cure rate at TOC in the mMITT population was 132 of 144 (91.7%; 95% CI, 86.3% to 95.4%) for CAZ-AVI and 129 of 137 (94.2%; 95% CI, 89.3% to 97.2%) for BAT. The per-patient favorable microbiological response rate in patients with cUTI treated with CAZ-AVI (n = 118 of 144, 81.9%; 95% CI, 75.1% to 87.6%) was higher than that with BAT (n = 88 of 137, 64.2%; 95% CI, 56.0% to 71.9%). Rates of clinical cure declined with time but remained ≥ 85% for the CAZ-AVI arm.

AEs occurred in 51 of 164 (31.1%) and 66 of 168 (39.3%) patients in the CAZ-AVI and BAT arms, respectively, with serious AEs in 5.5% and 6.0% of patients, respectively. The most frequent AEs were gastrointestinal disorders (12.8% and 17.9%, respectively). Seven deaths (3 in the CAZ-AVI arm and 4 in the BAT arm) were not considered related to the therapy.

The results indicate the potential value of CAZ-AVI in the treatment of cUTI caused by ceftazidime-resistant gram-negative bacteria. The small numbers of cIAI patients preclude any definitive conclusion about the efficacy of CAZ-AVI in treating this sort of infection.

New Antibiotic Combination for Treating Complicated Intra-abdominal Infections

Written by Jill Shuman

The growing prevalence of third-generation cephalosporin-resistant Enterobacteriaceae and *Escherichia coli* isolates throughout the world has caused an increase in the utilization of carbapenems. This has led to a resultant surge in carbapenem resistance and has presented an unmet need for antibiotics that will decrease the reliance on carbapenems for treating these infections.

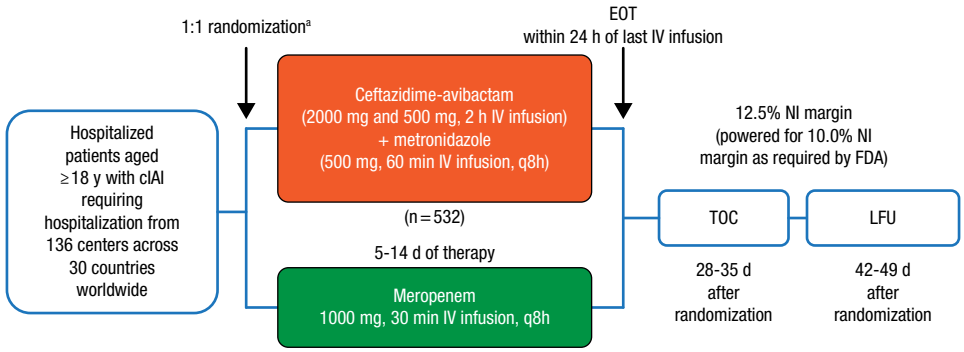
John E. Mazuski, MD, Washington University School of Medicine, St Louis, Missouri, USA, presented pooled data on 2 identical phase 3 studies: RECLAIM 1 [NCT01499290] and RECLAIM 2 [NCT01500239]. The 2 studies investigated the safety and efficacy of ceftazidime-avibactam (CAZ-AVI) plus metronidazole (MTZ) compared with meropenem (MER) in treating complicated intra-abdominal infections.

RECLAIM 1 and 2 originally enrolled 1149 adults with a diagnosis of complicated intra-abdominal infection from 30 countries between March 2012 and April 2014. Patients (n = 1066) were then randomized on a 1:1 basis to receive either CAZ-AVI plus MTZ (n = 532) or MER (n = 534) for 5 to 14 days (Figure 1). With agreement from both the European Medicines Agency and the FDA, the 2 studies were subsequently combined to form 1 global phase 3 study and analyzed using a single pooled data set. The primary end point of the trial was the clinical cure rate at the test-of-cure visit 28 to 35 days following randomization.

Noninferiority was assessed in the modified intention-to-treat (MITT; n = 1043) and clinically evaluable (n = 826) populations for the European Medicines Agency and the microbiologically modified intention-to-treat (mMITT) (n = 823) population for the FDA. The level of noninferiority was determined to be met if the lower limit of the 95% confidence interval for the between-group difference was > −12.50%. Adverse events (AEs) and serious AEs, including significant laboratory findings, were compared between groups in the safety population (n = 1058).

Clinical cure rates at test-of-cure visit in the MITT, clinically evaluable, and mMITT populations are summarized in Figure 2. Based on the preset definitions of inferiority,

Figure 1. Study Design: RECLAIM 1 and RECLAIM 2



APACHE, Acute Physiology and Chronic Health Evaluation; cIAI, complicated intra-abdominal infection; EOT, end of treatment; IV, intravenous; LFU, late follow-up; NI, noninferiority; TOC, test of cure.

[a]Stratified by baseline severity of disease (APACHE II score) and region.

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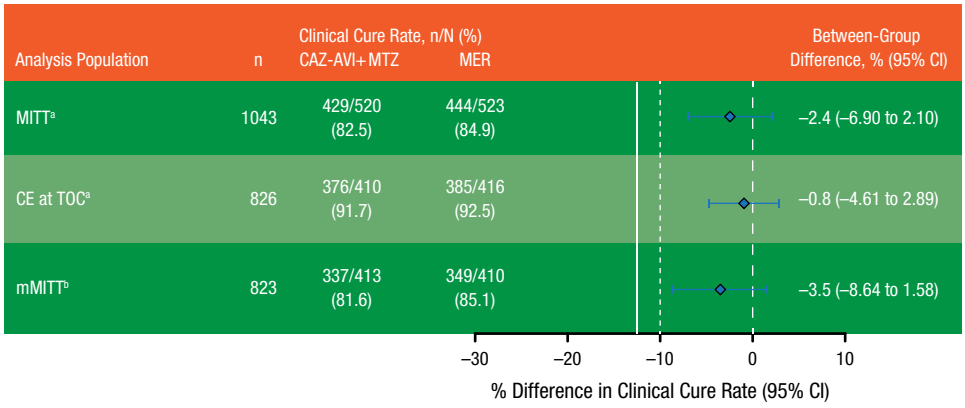
Figure 2. Primary Efficacy Results



Solid line represents sponsor prespecified noninferiority margin of –12.5% for the lower limit of the 95% CI. Dashed line represents FDA requirement of –10%.

CAZ-AVI+MTZ, ceftazidime-avibactam plus metronidazole; CE, clinically evaluable; MER, meropenem; MITT, modified intention to treat; mMITT, microbiologically modified intention to treat; TOC, test of cure.

[a]European Medicines Agency co-primary analysis population.

[b]FDA primary analysis population.

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CAZ-AVI plus MTZ was noninferior to MER in all populations. In the mMITT population, CAZ-AVI plus MTZ showed clinical activity in patients infected with CAZ-resistant pathogens, with a clinical cure rate of 83.0% vs 85.9% in patients receiving MER. The treatment difference in this subgroup was –3.0% (95% CI, –17.9% to 10.6%).

The rate of AEs with CAZ-AVI plus MTZ was 45.9%, compared with 42.9% with MER, with serious AE rates of 7.9% and 7.6%, respectively. The most frequently reported AEs following treatment with CAZ-AVI plus MTZ were diarrhea, nausea, vomiting, and fever.

Prof Mazuski highlighted a specific subgroup of patients with moderate renal impairment at baseline. The clinical cure rates in these patients were lower in the CAZ-AVI plus MTZ group compared with the MER group (48.8% vs 74.4%; between-group percentage, –25.6; 95% CI, –44.53 to –4.78). However, because approximately two-thirds of these patients showed rapid improvement in creatinine clearance within 48 to 72 hours of dosing, the lower cure rates may reflect underdosing of the CAZ-AVI plus MTZ group in the first critical days of the study. According to Prof Mazuski,

new dosing adjustments are forthcoming for patients with moderate renal impairment.

In summary, CAZ-AVI plus MTZ was noninferior to MER in the treatment of patients with complicated intra-abdominal infection and had a safety profile consistent with the known profiles of CAZ and MTZ. The combination therapy produced high response rates against key pathogens and against ceftazidime-resistant pathogens.

Subset Analyses of ASPECT-cIAI: Ceftolozane/Tazobactam Effective in cIAIs

Written by Emma Hitt Nichols, PhD

A major challenge in the treatment of complicated intra-abdominal infections (cIAIs), including secondary or tertiary peritonitis and cIAI associated with health care, is the potential that a resistant pathogen is responsible for the infection [Eckmann C, Shekarriz H. *Eur Infect Dis*. 2012]. In these settings, extended-spectrum β-lactamase (ESBL)–producing organisms and multidrug-resistant *Pseudomonas* are particularly prevalent. Treatment may be additionally complex in patients who are obese, as a result of obesity-associated factors such as decreased immune function or dysregulation, the presence of comorbidities, and respiratory dysfunction. Furthermore, the pharmacokinetics/pharmacodynamics of β-lactam antibiotics may be altered in patients who are obese [Pai MP, Bearden DT. *Pharmacotherapy*. 2007].

Two presentations reporting on different subsets of patients focused on the safety profile and efficacy of ceftolozane/tazobactam (TOL/TAZ) plus metronidazole (MTZ) in the treatment of cIAIs based on data from the ASPECT-cIAI trial [Solomkin J et al. *Clin Infect Dis.* 2015].

Christian Eckmann, MD, Academic Hospital of Medical University Hannover, Peine, Germany, presented data assessing TOL/TAZ plus MTZ compared with meropenem (MER) in European patients. TOL/TAZ, which is currently approved by the FDA for the treatment of complicated urinary tract infections and cIAIs, has demonstrated activity against *Pseudomonas aeruginosa* in vitro, including organisms with drug-resistant mechanisms [Farrell DJ et al. *Antimicrob Agents Chemother*. 2013]. While TOL/TAZ is active against some of the most common anaerobic pathogens encountered in cIAI, including *Bacteroides fragilis*, it is not active against all anaerobic pathogens; therefore, it must be used with MTZ in patients with cIAIs [Snydman DR et al. *Antimicrob Agents Chemother*. 2014].

In the international double-blind phase 3 ASPECT-cIAI trial, 993 adults with clinical evidence of cIAI were randomly assigned to receive TOL/TAZ 1.5 g plus MTZ 500 mg every 8 hours or MER 1 g every 8 hours intravenously for 4 to 14 days [Solomkin J et al. *Clin Infect Dis*. 2015]. Patients were excluded if the cIAI was managed by staged abdominal repair without closed fascia, the source control during surgery was likely inadequate, systemic antimicrobials were used to treat cIAI for >24 hours prior to initiation of study drug, the creatine clearance was <30 mL/min, and there was a presence of septic shock.

Patients (n=764) enrolled in European centers were analyzed. The mean age was 51.4 years, and about 56% of patients were men. At baseline, 51.5% of patients received prior antibiotic therapy, and the mean Acute Physiology and Chronic Health Evaluation II score was 6. Major anatomic locations of the cIAI included the appendix, biliary tract, small bowel, and colon.

At the test-of-cure visit (24 to 32 days from start of therapy), the overall clinical cure rates were similar between treatment arms, with a weighted difference of 0.6 (99% CI, –3.99 to 5.13) in the clinically evaluable population. However, the clinical cure rates differed among the treatment arms according to pathogen (Table 1). TOL/TAZ plus MTZ treatment resulted in greater clinical cure rates in patients infected with *Klebsiella pneumonia,* ESBL-producing *Klebsiella pneumoniae,* and *P aeruginosa* compared with MER. In contrast, MER treatment resulted in higher clinical cure rates in patients infected with *Enterobacter cloacae* compared with TOL/TAZ treatment.

Treatment-emergent adverse events (TEAEs) occurred more frequently in the TOL/TAZ plus MTZ arm compared with the MER arm (36.9% vs 34.5%). Common TEAEs included nausea, vomiting, diarrhea, pyrexia, hypokalemia, and insomnia. Serious TEAEs occurred in 7% of patients in the TOL/TAZ arm and 4.7% of patients

Table 1. Clinical Cure Rates According to Pathogen in European Patients in ASPECT-cIAI

Pathogen	TOL/TAZ + MTZ	MER
Escherichia coli	95.7	91.4
ESBL + *E coli*	100	100
Klebsiella pneumoniae	95	83.3
ESBL + *K pneumoniae*	100	75
Pseudomonas aeruginosa	100	95.8
Proteus mirabilis	88.9	88.9
Enterobacter cloacae	89.5	100

Data presented in percentages.

ESBL, extended-spectrum β-lactamase; MER, meropenem; MTZ, metronidazole; TOL/TAZ, ceftolozane/tazobactam.