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

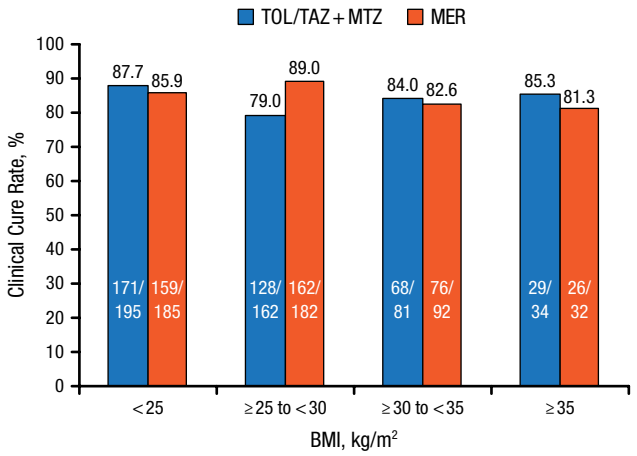
Table 1. Clinical Cure Rates According to Pathogen in European Patients in ASPECT-cIAI

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.

Figure 1. Clinical Cure Rates in ASPECT-cIAI According to BMI



BMI, body mass index; MER, meropenem; MTZ, metronidazole; TOL/TAZ, ceftolozane/tazobactam.

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in the MER arm. In the TOL/TAZ and MER arms, 9 and 5 deaths occurred, respectively; however, the investigators determined that the deaths were due to treatment failures for unrelated conditions or were indeterminate and not associated with the study drugs. In the study, 10 (2.7%) and 7 (1.8%) of patients who received TOL/TAZ and MER, respectively, discontinued the study due to TEAEs.

In conclusion, Prof Eckmann stated that the data from the ASPECT-cIAI trial suggest that treatment of cIAI with TOL/TAZ plus MTZ resulted in high clinical cure rates, with greater success than MER for the pathogen *P aeruginosa* and many Enterobacteriaceae, including ESBL-positive strains.

Benjamin Miller, PharmD, Cubist Pharmaceuticals, Lexington, Massachusetts, USA, presented a post hoc analysis of the ASPECT-cIAI trial assessing clinical response in nonobese and obese patients. Of the total patients in the trial, 239 were considered obese, with a mean body mass index (BMI) of 32.9 kg/m^2.

The clinical cure rates with TOL/TAZ treatment were somewhat lower vs MER in patients who were nonobese (BMI < 30; 83.8% vs 87.5%), whereas they were higher in patients who were obese (BMI ≥ 30; 84.3% vs 82.3%). In addition, TOL/TAZ treatment appeared to be least effective in patients with a mean BMI of ≥ 25 to < 30 kg/m^2 (Figure 1). However, Dr Miller concluded that, overall, TOL/TAZ efficacy and safety outcomes were similar between nonobese and obese patients.

The most common TEAEs in obese and nonobese patients included diarrhea, nausea, vomiting, and pyrexia, with diarrhea and nausea occurring more commonly in obese patients in the TOL/TAZ plus MTX arm vs the MER arm.

To conclude, BMI had no impact on clinical outcomes in patients treated with TOL/TAZ plus MTZ. With the exception of diarrhea and nausea in the obese subset, TEAEs were comparable between the 2 treatment arms.

Ceftolozane/Tazobactam Safe and Effective Against Complicated UTIs and Pyelonephritis

Written by Rita Buckley

Antimicrobial resistance to gram-negative pathogens is increasing. Hospital-acquired urinary tract infections (UTIs) are increasingly resistant to the antibiotics used to treat them, including the fluoroquinolones [Tandogdu Z et al. *World J Urol.* 2014]. Nonetheless, fluoroquinolones, including high-dose levofloxacin, are recommended as first-line therapy in clinical guidelines and remain the most widely used antibacterials to treat complicated urinary tract infection (cUTI) and pyelonephritis.

Ceftolozane/tazobactam (TOL/TAZ) is a novel cephalosporin combined with a β-lactamase inhibitor, and it has been shown to have in vitro activity against *Pseudomonas aeruginosa* and gram-negative pathogens, including most extended-spectrum β-lactamase (ESBL)–positive strains. This fixed-dose combination (in a 2:1 ratio) has been approved by the FDA to treat complicated intraabdominal infections and cUTIs, including pyelonephritis; an application has been submitted to the European Medicines Agency for these indications.

Florian M. Wagenlehner, MD, PhD, Justus-Liebig University, Giessen, Germany, presented findings from a European subgroup analysis of the ASPECT-cUTI trial [Wagenlehner FM et al. *Lancet.* 2015] that indicated that TOL/TAZ vs levofloxacin was safe and effective for the treatment of cUTIs, including pyelonephritis.

The ASPECT-cUTI trial was a double-blind phase 3 noninferiority trial conducted in 209 centers in 25 countries, and the results of the main study have been reported [Wagenlehner FM et al. *Lancet.* 2015]. The trial randomized men and women aged ≥ 18 years who were hospital inpatients between July 2011 and September 2013 in a 1:1 ratio to receive intravenous TOL/TAZ 1.5 g every 8 hours (n = 543) or intravenous high-dose levofloxacin 750 mg QD (n = 540) for 7 days.

The inclusion criteria included presence of pyuria, ≥ 2 clinical signs or symptoms of pyelonephritis or cUTI, and a pretreatment baseline urine culture specimen