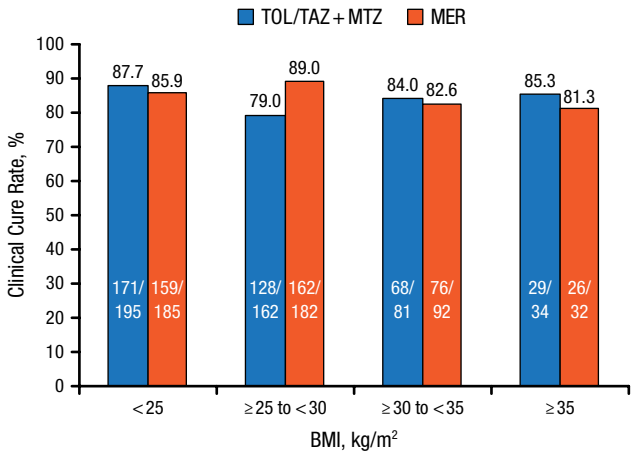
Figure 1. Clinical Cure Rates in ASPECT-cIAI According to BMI



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

obtained within 36 hours of the first dose of the study drug. Patients were excluded if they received a nonstudy antibiotic within 48 hours of the baseline urine specimen or had renal impairment (a creatinine clearance <30 mL/min).

The primary end point of the ASPECT-cUTI trial was the composite of microbiological eradication (ME) and clinical cure at the test-of-cure visit 5 to 9 days after the end of therapy in the patients who were microbiologically evaluable (modified intention-to-treat population). The main study found that TOL/TAZ was noninferior to levofloxacin for the primary end point (76.9% vs 68.4%). While the study was not powered to test superiority, the results indicated that TOL/TAZ was also superior to levofloxacin. The mean age of the patients was 47 years; 72% were women; and about 82% had pyelonephritis at study entry.

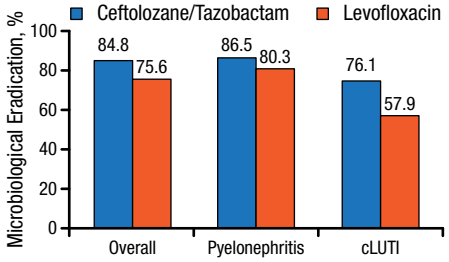
The European subgroup analysis was conducted to evaluate the primary end point, outcomes in patients with drug-resistant pathogens, and the safety of TOL/TAZ in the patients enrolled in Europe. Of the 812 patients, 544 qualified for the microbiologically evaluable population; 269 had been randomized to TOL/TAZ and 275 to levofloxacin. Demographic and baseline characteristics for the microbiologically evaluable population were similar between the 2 treatment groups.

The ME rate for the main study was 84.7% with TOL/TAZ and 75.4% with levofloxacin (9.4% difference; 99% CI, 1.5% to 17.1%). In the European analysis, the ME rates for the overall cohort and for patients with pyelonephritis were similar to that in the main study and were slightly lower in the patients with cUTI (Figure 1).

At baseline, the most frequent organism was *Escherichia coli*, in 78.6% of patients in the main study and 76.5% in the European subgroup; of these patients, 13% and 10%, respectively, were considered to be *E coli* ESBL producers. TOL/TAZ compared with levofloxacin had higher rates of ME against *E coli* (90% vs 78.6%), *Klebsiella pneumoniae* (81% vs 55%), *Proteus mirabilis* (100% vs 72.7%), and *Pseudomonas aeruginosa* (83.3% vs 45%), while it was the opposite for *Enterobacter cloacae* (33.3% vs 100%). TOL/TAZ had substantial rates of ME against drug-resistant pathogens compared with levofloxacin (Table 1).

The incidence of adverse events (AEs) and serious AEs was similar between the TOL/TAZ group (27.5% and 2.0%) and the levofloxacin group (26.5% and 2.2%, respectively). More patients discontinued the study drug because of an AE in the levofloxacin group (2.0%) vs the TOL/TAZ group (1.0%).

Figure 1. Microbiological Response by Diagnosis in European Analysis



	Ceftolozane/Tazobactam, n/N (%)	Levofloxacin, n/N (%)	Percentage Difference (95% CI)
Overall	228/269 (84.8)	208/275 (75.6)	9.1 (2.4 to 15.7)
Pyelonephritis	193/223 (86.5)	175/218 (80.3)	6.3 (–0.7 to 13.2)
cLUTI	35/46 (76.1)	33/57 (57.9)	18.2 (–0.2 to 34.5)

cLUTI, complicated lower-urinary tract infection.

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Table 1. Efficacy Against Drug-Resistant Pathogens

	ESBL-Producing Pathogens (n = 68; 12.5%)			Levofloxacin-Resistant Pathogens (n = 139; 25.9%)		
	Ceftolozane/Tazobactam	Levofloxacin	95% CI	Ceftolozane/Tazobactam	Levofloxacin	95% CI
Overall cohort	67.6	41.9	2.0 to 45.8	62.9	37.7	8.5 to 40.1
Pyelonephritis	63.3	55.6	–18.9 to 34.2	62.8	44.4	–1.6 to 36.2
cUTI	85.7	23.1	16.7 to 81.6	63.2	21.7	11.5 to 62.8

Data presented in percentages.

cUTI, complicated urinary tract infection; ESBL, extended-spectrum β-lactamase.