

# Heterogeneity of Recent Phase 3 Complicated Urinary Tract Infection Clinical Trials

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**Background.** For new antibiotics developed to treat antibiotic-resistant Gram-negative infections, the US Food and Drug Administration (FDA) regulatory pathway includes complicated urinary tract infection (cUTI) clinical trials in which the clinical isolates are susceptible to the active control. This allows for inferential testing in a noninferiority study design. Although complying with regulatory guidelines, individual clinical trials may differ substantially in design and patient population. To determine variables that impacted patient selection and outcome parameters, 6 recent cUTI trials that were pivotal to a new drug application (NDA) submission were reviewed.

**Methods.** This selective descriptive analysis utilized cUTI trial data, obtained from publicly disclosed information including FDA documents and peer-reviewed publications, from 6 new antibiotics developed to treat multidrug-resistant Gram-negative infections: ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, ceftiderocol, plazomicin, and fosfomycin. Eravacycline was not approved for cUTI and is not included.

**Results.** Microbiologic modified intent-to-treat sample size, age, proportions of female patients, acute pyelonephritis (AP), *Escherichia coli* and other pathogens at baseline, protocol-specified switch to oral antibiotic, and the noninferiority margin were compared. Outcome data included clinical response, microbiologic eradication, and composite outcomes, including a subset of patients with AP.

**Conclusions.** A study design can follow regulatory guidelines but still have variable populations. The proportion of AP within a study varied greatly and influenced population demographics (age, gender) and baseline microbiology. A smaller proportion of AP resulted in an older patient population, fewer females, less *E coli*, and lower proportions of patients achieving success. Fluoroquinolones and piperacillin/tazobactam should be reconsidered as active comparators given the high rates of resistance to these antibiotics.

**Keywords.** acute pyelonephritis; carbapenem resistance; cUTI; study design.

Antibiotic resistance is a global problem that is spreading at an astonishing rate and poses a great threat to humankind. More than 2.8 million people acquire serious infections with bacteria that are resistant to 1 or more of the antibiotics designed to treat those infections annually in the United States [1]. At least 35 000 people die each year as a direct result of these antibiotic-resistant infections, and many others perish from other conditions complicated by an antibiotic-resistant infection [1]. In addition, the estimated economic cost of antibiotic resistance to the American economy ranges from \$20 billion in excess direct healthcare costs, with additional costs to society for lost productivity as high as \$35 billion a year (2008 dollars) [2, 3]. Some of the antibiotic resistance identified and categorized by the Centers for

Disease Control and Prevention (CDC) as either “serious” or “urgent” include the spread of extended-spectrum  $\beta$ -lactamase (ESBL)-producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Acinetobacter*, and multidrug-resistant (MDR) *Pseudomonas aeruginosa* infections [1]. These same pathogens have been identified by the World Health Organization (WHO)’s global priority list as “Priority 1” and “Critical” [4]. The CDC and the WHO have identified the development of new antibiotics as one of the strategies to help address infections due to antibiotic-resistant organisms [1, 4]. Enterobacterales are the most common bacteria causing cUTI, and infections due to MDR organisms within this bacterial family can be characterized as fluoroquinolone-resistant (FQR), broad-spectrum cephalosporin-resistant, or carbapenem-resistant (CR). Although carbapenems can be used to treat FQR- and ESBL-producing organisms, there are limited options for CRE [5, 6]. The mortality associated with CRE infections, including bacteremia, may be as high as 20% to 54.3%, which further underscores the need for better available treatment options [6–9].

One challenge for pharmaceutical companies as they develop new antibiotics to treat MDR or extensive drug-resistant (XDR)

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infections is the need for interpretable clinical trial data, which requires inferential (statistical) testing of a prespecified efficacy hypothesis. The acceptable study is a noninferiority design that excludes organisms known to be resistant to the active control treatment. Until the recent approval of antibiotics capable of treating CR pathogens, this feature of equipoise often excluded the very types of infections that the new antibiotics were being developed to treat.

To facilitate the development of new antibiotics to treat MDR/XDR Gram-negative infections, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have endorsed a streamlined development pathway with limited clinical trial requirements. A single study in cUTI with a less robust noninferiority margin (15%) supported by pharmacokinetic/pharmacodynamic data and a minimum of 300 patients treated with the investigational product (IP) may be sufficient for a “limited use” indication in cUTI.

To further facilitate enrollment of patients into cUTI clinical trials, the FDA and EMA have recently allowed (1) prior antibiotic use for up to 24 hours in a proportion (<25%) of study patients and (2) for investigational antibiotics with only a parenteral formulation and the ability to switch to a noninvestigational oral antibiotic. This results in variability of the timing of the primary efficacy endpoint to a fixed day (usually day 5) when the patient is still receiving the IP, rather than the traditional test of cure (TOC) approximately 1 week after the last dose of the study drug. Another important variable is the selection of the active control antibiotic, which may or may not be suitable for current study patient populations. These differences in treatment regimens and primary endpoints make direct comparison of clinical trials for cUTI more difficult. The intention of this analysis was to highlight the current cross-study differences and to recognize and correct for this variability in future trials.

## METHODS

Six recent clinical trials that supported FDA or EMA regulatory review for the indication of cUTI including pyelonephritis have been analyzed in a selected descriptive approach. Data were obtained from publicly disclosed information and the following hierarchy was utilized: (1) US Prescribing Information, (2) FDA Medical Review, and (3) peer-reviewed publications. Acute uncomplicated pyelonephritis (AUP) was defined as pyelonephritis with normal urinary tract anatomy and the presence of clinical signs and symptoms of upper urinary tract involvement. Unless otherwise specified, it was assumed that AP is the same or closely approximated AUP. Two studies, RECAPTURE (cefazidime-avibactam) and APEKScUTI (cefiderocol), included patient self-assessment questionnaires to compare with physician assessment (Patient Symptom Assessment

Questionnaire [PSAQ] and Structured Patient Interview [SPI], respectively). Neither were validated, patient-reported outcome instruments.

Complicated UTI is defined as a urinary tract infection with pyuria and a documented microbial pathogen, which is usually accompanied by local and systemic signs and symptoms. These concomitantly occur in the presence of a functional or an anatomical abnormality of the urinary tract or in the presence of catheterization. Acute pyelonephritis and AUP are identified as a subset of cUTI.

## RESULTS

Ceftolozane-tazobactam ([TOL-TAZ] ASPECT-cUTI) [10] and ceftazidime-avibactam ([CAZ-AVI] RECAPTURE) [11] trials followed a traditional development plan in which the noninferiority margin was 10%. The remaining 4 investigational studies (meropenem-vaborbactam [MER-VAB], TANGO-1 [12]; plazomicin [PLZ], EPIC [13, 14]; cefiderocol [CFDC], APEKS-cUTI [15]; IV fosfomycin [FOS], ZEUS [16, 17]) were subject to streamlined development “flexibility” and had a noninferiority margin of 15%. Patient populations differed based on the proportion of AP or AUP, which resulted in more females, younger age, higher proportion of *Escherichia coli*, and higher success for the composite endpoint of clinical cure and microbiologic eradication. The percentage of randomized patients with a qualifying bacterial pathogen ( $\geq 10^5$  colony-forming units/mL) identified at baseline (ie, micro-ITT population) ranged from 64.2% in the EPIC trial to 82.8% in the APEKS-cUTI trial. The gender distribution in the EPIC and APEKS-cUTI trials was almost equivalent, reflecting the lower proportion of subjects with AP or AUP (41.8% and 27%, respectively), compared with the other 4 contemporary cUTI studies in which AP, which is predominantly seen in younger females, often contributed to the majority of study participants. Patient population with AP/AUP ranged from 27% in the APEKS- trial to 82% in the ASPECT-cUTI trial. *Escherichia coli* was the predominant pathogen at baseline in all studies, but it ranged from 62.3% in the APEKS-cUTI trial to 78.6% in the ASPECT-cUTI trial, and it was inversely related to the proportion of AP/AUP. *Pseudomonas aeruginosa* ranged from 0 to 6.2% (Table 1). The proportion of patients with resistance to the control antibiotic of the baseline pathogen varied greatly (2.6%–26.5%) and was related to the choice of the active control antibiotic.

All studies met the prespecified criteria for noninferiority (10% or 15%), and, despite the noninferiority study design, 4 of 6 trials demonstrated statistical superiority for the composite endpoint at TOC, which was driven by better microbiologic eradication at TOC for the investigational drug. Microbiologic eradication at TOC (range, 56.2%–89.5%) was highly variable and considerably lower than eradication at EOT (range, 84.6%–97.9%). Three of the 6 studies permitted switch-to-oral

**Table 1. Baseline Demographics and Study Design**

	(TOL/TAZ) ASPECT-cUTI [10]	(CAZ/AVI) RECAPTURE [11]	(MER-VAB) TANGO-1 [12]	Plazomicin EPIC [13, 14]	Cefiderocol APEKS-cUTI [15]	IV Fosfomycin ZEUS [16, 17]
Safety ITT population (randomized and treated) (N)	1068	1020	545	609	448	464
mMITT (N)	800	810	374	388	371	362
% of Safety Population	74.9	79.4	68.6	64.2	83.0	78.0
Patient Population						
Female (%)	74	69.8	66.0	52.8	55	63.5
Age (mean)	50.5	52.4	54.0	59.4	62	49.9
Age ≥65 years (%)	25	31.1	37.0	49.5	55	34.5
AP/AUP (%)	82	72/62	59	41.8	27	53
Pathogens at Baseline						
<i>Escherichia coli</i> (%)	78.6	73.8	64.7	67.8	62.3	73.4
<i>Pseudomonas aeruginosa</i> (%)	2.9	4.7	3.7	0	6.2	4.7
Pathogens at baseline resistant to comparator drug (%)	26.5	3.0	12.0	2.6	3.2	5.1
Comparator study drug and dose	Levofloxacin 750 mg Q24H	Doripenem 500 mg Q8H	PIP/TAZ 4.5 g Q8H	Meropenem 1 g Q8H	IMI/CS 1 g Q8H	PIP/TAZ 4.5 g Q8H
Randomization	1:1	1:1	1:1	1:1	2:1	1:1
Switch from IV to PO	No	Yes	Yes	Yes	No	No
Duration of IV therapy (median)	6.7 days (both groups)	7 days (CAZ/AVI) 8 days (doripenem)	8 days (both groups)	6 days (both groups)	9 days (both groups)	~7 days
Noninferiority margin (%) (FDA)	10%	10%	15%	15%	15%	15%

Abbreviations: AP, acute pyelonephritis; AUP, acute uncomplicated pyelonephritis; CAZ/AVI, ceftazidime/avibactam; cUTI, complicated urinary tract infection; FDA, US Food and Drug Administration; IMI/CS, imipenem/cilastatin; ITT, intent-to-treat; IV, intravenous; MER/VAB, meropenem/vaborbactam; mMITT, microbiologic modified intent-to-treat; NA, not applicable; PIP/TAZ, piperacillin/tazobactam; TOL/TAZ, ceftolozane/tazobactam.

treatment. In studies in which switch-to-oral therapy was not allowed, the duration of therapy of the investigational antibiotic was 7–9 days compared with 6–8 days where oral switch was allowed. The combined clinical response and microbiologic eradication at TOC was generally similar for all investigational drugs, but these varied for the comparator drugs, resulting in considerable treatment differences and demonstration of statistical superiority for the investigational drug in 4 of 6 studies (Table 2). All comparator drugs used in each of the studies used the FDA-approved dosing per indication; however, due to increasing antibiotic resistance, studies in which an FQ (levofloxacin in the ASPECT trial) or PIP/TAZO (in TANGO 1 and ZEUS) enrolled patients with baseline pathogen resistant to the control drug was 26% and 12% and 5.1%, respectively, whereas in studies using a carbapenem as the active control, the proportion enrolled with carbapenem resistance was <4%.

All treatment arms from the 6 studies had rates of microbiological eradication at end of treatment (EOT) exceeding 92%, with the exception of the levofloxacin arm in ASPECT (84%), which reflected the high rates of levofloxacin resistance at baseline. However, at TOC, recurrence of the baseline pathogen was common, reflecting lower overall success at this traditional time point for efficacy analysis. For the composite endpoint of clinical cure and microbiologic eradication, the range was 54.5%–73.2% for the active comparators and 64.7%–81.7% for the investigational antibiotics.

A consistent finding in all studies was the higher composite success and microbiological eradication in patients with AP/AUP compared with overall study population response rate. In addition, in all cases, the response reported with the investigational drug for AP/AUP was higher than the control drug.

## DISCUSSION

Complicated UTI is defined as a clinical syndrome characterized by pyuria and a documented microbial pathogen, identified either through a urine or blood culture, and accompanied by local and/or systemic signs and symptoms. These may include dysuria, urinary frequency, suprapubic pain, fever, chills, malaise, flank pain, and/or tenderness that occur (1) in the presence of a functional or an anatomical abnormality of the urinary tract or (2) in the presence of catheterization. Patients with infection involving the upper urinary tract, ie, the kidney, are considered to have pyelonephritis. Patients with acute pyelonephritis, regardless of the presence of an underlying urinary tract abnormality, are considered a subset of patients with cUTI [18, 19]. However, these patients are not always well defined in clinical trials. It is notable that all 6 studies reviewed followed the FDA- and EMA-specific criteria for the diagnosis and definition of eradication. Acute pyelonephritis is generally referred to as an acute infection occurring in a patient without host factors defining a cUTI, for example, urinary tract obstruction,

**Table 2. Clinical and Microbiological Outcomes by Study (%)**

	(TOL/TAZ) ASPECT-cUTI	(CAZ/AVI) RECAPTURE	(MER-VAB) TANGO-1	Plazomicin EPIC	Cefiderocol APEKS-cUTI	IV Fosfomycin ZEUS
Combined clinical response and microbiological eradication at TOC	76.9 vs 68.4	71.2 vs 64.5	76.5 vs 73.9	81.7 vs 70.1	72.6 vs 54.6	64.7 vs 54.5
Treatment difference (95% CI)	8.5 (2.3–14.6)	6.7 (0.30–13.1)	3.3 (–6.2 to 13.0)	11.6 (2.7–20.3)	18.6 (8.23–28.92)	10.2 (–0.4 to 20.8)
Microbiologic eradication at EOIV/end of therapy	95.2 vs 84.6	95.2 vs 94.7	97.9 vs 92.3	97.4 vs 97.5	96.8 vs 95.8	Not reported
Treatment difference (95% CI)	10.5 (6.6–14.9)	0.4 (–2.7 to 3.56)	5.6 (1.4–10.7)	–0.1 (–4.1 to 3.9)	1.1 (–3.03 to 5.25)	
Microbiological eradication at TOC	80.4 vs 72.1	77.4 vs 71.0	68.8 vs 62.1	89.5 vs 74.6	73.3 vs 56.3	65.8 vs 56.2
Treatment difference (95% CI)	8.3 (2.4–14.1)	6.4 (0.3–12.4)	6.7 (–3.0 to 16.2)	14.9 (7.0–22.7)	17.3 (6.92–27.58)	9.6 (–1.0 to 20.1)
Clinical response at TOC	92.0 vs 88.6	90.3 vs 90.4	90.6 vs 86.3	89.0 vs 90.4	89.7 vs 87.4	90.8 vs 91.6
Treatment difference (95% CI)	3.4 (–0.7 to 7.6)	–0.1 (4.23–4.03)	4.4 (–2.2 to 11.1)	–1.4 (–7.9 to 5.2)	2.4 (–4.66 to 9.44)	–0.8 (–7.2 to 5.6)
Microbiological eradication at LFU (EOT +14 days)	70.7 vs 81.3	68.2 vs 60.9	68.8 vs 56.5	84.3 vs 65.0	57.1 vs 43.7	Not reported
Treatment difference (95% CI)	–10.6 (25.9–6.1)	7.3 (0.68–13.81)	12.2 (2.4–21.8)	19.3 (10.4–27.9)	13.9 (3.21–24.63)	
Composite endpoint for AP/AUP at TOC	79.0 vs 73.2	NR	82.5 vs 75.2	85.7 vs 71.8	83 vs 69	67.7 vs 66

Abbreviations: AP, acute pyelonephritis; AUP, acute uncomplicated pyelonephritis; CI, confidence interval; cUTI, complicated urinary tract infection; EOIV, end of IV therapy; EOT, end of therapy; LFU, long-term follow-up; TOC, test of cure.

stones, cancer, or bladder catheterization [18, 20]. However, patients with a cUTI may also have involvement of the kidney, thus there are 2 different populations with AP: those with or without host factors constituting cUTI. In the setting of clinical studies to support new investigational antibiotics, all identified AP as a separate population from cUTI. Only 1 study, APEKS-cUTI, made a clear distinction between AUP and cUTI with or without pyelonephritis, at the time of randomization. Other studies provided post hoc categorization of AP with or without an anatomic abnormality to qualify as cUTI. Due to this heterogeneity of infection types, cross-study comparisons of efficacy results are compromised because there are several variables that affect the outcomes.

The proportion of a study population that has AUP can influence the outcome because these infections occur in younger patients, usually female, with pathogens more likely to be antibiotic-susceptible *E coli*, resulting in higher clinical and microbiologic response rates [21]. The high recurrence rate after the EOT in patients with cUTI is not unexpected and is likely due to irreversible host factors defining cUTI such as renal or bladder calculi, cancer, or indwelling bladder catheters, all of which provide a nidus for biofilm-forming pathogens [20].

Based on the comparisons of these recent cUTI clinical trials for new antibiotic approvals, the suitability of fluoroquinolones or piperacillin/tazobactam as comparators should be questioned. Initial patient randomization and treatment occurs before the full identification and susceptibility of the causative pathogen is known. As antibacterial resistance continues to increase, the relevance of some active control treatments should be questioned. With the recent approval of several new antibiotics with activity against FQR-producing, ESBL-producing, and CR Enterobacterales, future studies should consider using one of these agents as the active control. This would allow CR organisms to be enrolled, thus making study recruitment easier and the outcomes more relevant to the current need for new antibiotics.

This analysis of recent cUTI clinical trials has several strengths. All are contemporary randomized, double-blinded prospective studies using similar inclusion or exclusion criteria. All met the prespecified criteria for noninferiority even for the more robust 10% noninferiority margin required for traditional approval. This comparison study does demonstrate the impact of the proportion of AP in the study population on patient demographics, baseline microbiology, and clinical and microbiological outcomes.

The main weakness of the study is the assumption made defining AP. Only the APEKS-cUTI and the APECT study clearly differentiated AUP from cUTI with upper tract involvement. However, given the general understanding for what constitutes AP and the evidence from the patient demographics (age, gender) and baseline pathogens, the majority of AP are assumed to be AUP. Limitations in the enrollment of AUP in the clinical

trial provide a patient population that is older and more gender equal and may provide a more appropriate population for the treatment of patients with MDR/XDR cUTIs.

## CONCLUSIONS

Clinical trials in cUTI, even when they serve the same regulatory and formulary decision-making objectives, are not the same. This review was not intended to demonstrate that any drug was better. Different endpoints and patient populations are influenced by study design (switch to oral) and the proportion of patients with AP. The wide range of AP diagnoses suggests that some studies enrolled more difficult-to-treat patients who are at greater risk of an infection caused by MDR pathogens. Paradoxically, those trials with a lower proportion of AUP were better able to demonstrate a treatment benefit (superiority) for microbiologic eradication for the investigational drug (eg, cefiderocol and plazomicin) in a more clinically challenging situation. Finally, not all antibiotics currently approved for cUTI are suitable for noninferiority studies in cUTI, given the current high rates of FQR- and ESBL-producing Enterobacterales. It is fortunate that the recent approval of several new antibiotics for cUTI provides a new standard for active control treatment.

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