Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

Florian M Wagenlehner, Obiamiwe Umeh, Judith Steenbergen, Guojun Yuan, Rabih O Darouiche

Summary

Background Treatment of complicated urinary-tract infections is challenging due to rising antimicrobial resistance. We assessed the efficacy and safety of ceftolozane-tazobactam, a novel antibacterial with Gram-negative activity, in the treatment of patients with complicated lower-urinary-tract infections or pyelonephritis.

Methods ASPECT-cUTI was a randomised, double-blind, double-dummy, non-inferiority trial done in 209 centres in 25 countries. Between July, 2011, and September, 2013, hospital inpatients aged 18 years or older who had pyuria and a diagnosis of a complicated lower-urinary-tract infection or pyelonephritis were randomly assigned in a 1:1 ratio to receive intravenous 1·5 g ceftolozane-tazobactam every 8 h or intravenous high-dose (750 mg) levofloxacin once daily for 7 days. The randomisation schedule was computer generated in blocks of four and stratified by study site. The next allocation was obtained by the study site pharmacist via an interactive voice-response system. The primary endpoint was a composite of microbiological eradication and clinical cure 5–9 days after treatment in the microbiological modified intention-to-treat (MITT) population, with a non-inferiority margin of 10%. This study is registered with ClinicalTrials.gov, numbers NCT01345929 and NCT01345955.

Findings Of 1083 patients enrolled, 800 (73·9%), of whom 656 (82·0%) had pyelonephritis, were included in the microbiological MITT population. Ceftolozane-tazobactam was non-inferior to levofloxacin for composite cure (306 [76·9%] of 398 *vs* 275 [68·4%] of 402, 95% CI 2·3–14·6) and, as the lower bound of the two-sided 95% CI around the treatment difference was positive and greater than zero, superiority was indicated. Adverse event profiles were similar in the two treatment groups and were mainly non-serious.

Interpretation Treatment with ceftolozane-tazobactam led to better responses than high-dose levofloxacin in patients with complicated lower-urinary-tract infections or pyelonephritis.

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Introduction

The urinary tract is a common source of life-threatening infections, and an important cause of sepsis in patients admitted to hospital wards, emergency departments, and intensive care units.[1] Urosepsis is associated with mortality of 20–40% in critically ill patients.[2] Treatment of complicated urinary-tract infections, which can affect the lower urinary tract or upper urinary tract (pyelonephritis), is becoming increasingly challenging because of extending antimicrobial resistance; most uropathogens implicated in health-care-associated complicated urinary-tract infections, including catheter-related infections, are resistant to multiple antimicrobial agents.[3–6] Worldwide, fluoroquinolones are the most frequently used antibacterials for the treatment of complicated urinary-tract infections (26·7%), followed by cephalosporins (23·3%), aminoglycosides (14·1%), and penicillins (13·8%), despite global resistance rates being 35–50% for these antibiotics.[3] Importantly, inappropriate or inadequate treatment of these common infections can result in poor clinical outcomes and place substantial burden on the health-care system.[7–9] Furthermore, patients with complicated urinary-tract infections caused by extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* spp are more likely to receive inappropriate antibiotics, have longer hospital stays, and incur higher costs than patients infected with other uropathogens.[8]

Ceftolozane-tazobactam is a novel cephalosporin combined with an established β-lactamase inhibitor that was developed to address the rising rates of antimicrobial resistance in Gram-negative pathogens.[10] This drug has potent in-vitro activity against multidrug-resistant strains of *Pseudomonas aeruginosa* and other common Gram-negative pathogens, including most ESBL-producing *Enterobacteriaceae* spp.[11,12] Ceftolozane-tazobactam is being studied for the treatment of serious infections, including complicated urinary-tract infections, complicated intra-abdominal infections, and nosocomial pneumonia.

In the Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Urinary Tract Infections (ASPECT-cUTI) clinical programme, the

efficacy and safety of ceftolozane-tazobactam were compared with those of levofloxacin, a widely used antibacterial, in hospital inpatients with complicated lower-urinary-tract infections or pyelonephritis. International guidelines recommend 500 mg levofloxacin as first-line empirical therapy in patients with all complicated urinary-tract infections.[13,14] 750 mg levofloxacin once daily for 5 days was shown in a randomised clinical trial to be non-inferior to 10 days of ciprofloxacin in adults.[15] Although there is no evidence-based consensus on duration of therapy for complicated urinary-tract infections, including pyelonephritis, Sandberg and colleagues[16] showed that 7 days was non-inferior to 14 days of treatment for acute pyelonephritis. On the basis of these findings, we chose a high-dose, extended-duration regimen for levofloxacin to ensure a clinically relevant and potentially highly effective comparator arm.

Methods

Study design

Two randomised, double-blind trials were started in July, 2011, at 209 sites worldwide, with identical protocols except for geography. Patients were enrolled in Eastern Europe (Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Moldova, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, and Ukraine), North America (Mexico and USA), South America (Brazil, Chile, Colombia, and Peru), and India, Israel, South Africa, South Korea, and Thailand (appendix). The trials were approved by relevant regulatory agencies and local institutional review boards, and were done in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent. In 2012, midway into enrolment, the US Food and Drug Administration released draft guidance that recommended a single-study pathway for approval of antibiotics in complicated urinary-tract infections and complicated intra-abdominal infections.[17] The study funder sought and received permission from the relevant regulatory agencies to pool the data from the two trials into one dataset. Enrolment in the two trials was completed in September, 2013, and the data were pooled after the database was locked in each study.

See Online for appendix

Study population

Eligible patients were aged 18 years or older, had pyuria (white blood cell count greater than $0{\cdot}01\times10^9$/L in unspun urine or $0{\cdot}01\times10^9$/L or more white blood cells per high-power field in spun urine), a diagnosis of pyelonephritis or complicated lower-urinary-tract infections, had been admitted to hospital for intravenous antibiotic therapy, and had a pretreatment baseline urine culture specimen obtained within 36 h before the first dose of study drug. Pyelonephritis was defined by the presence of two or more of the following symptoms: fever (oral temperature higher than 38°C) accompanied by rigors, chills, or warmth; flank pain; costovertebral angle or suprapubic tenderness on physical examination; or nausea or vomiting. Complicated lower-urinary-tract infections included all these symptoms plus suprapubic pain, dysuria, urinary frequency or urgency, and at least one of the following: male sex with urinary retention, indwelling urinary catheter, current obstructive uropathy, or any functional or anatomical urogenital-tract abnormality.[17] Patients were excluded if they had concomitant infections that required treatment with non-study antibacterial agents that had Gram-negative activity, an infection at baseline that the investigator determined would require more than a 7-day course of treatment, or a violation of the antibiotic restriction criteria (ie, received non-study antibiotic within 48 h before baseline urine culture or after urine sample collection but before the first dose of study drug). Full inclusion and exclusion criteria are provided in the appendix.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive ceftolozane-tazobactam or levofloxacin. The randomisation schedule was computer generated in blocks of four and stratified by study site. The study site pharmacist or designated staff member obtained the next allocation via an interactive voice-response or web-response system. Double-dummy saline infusions were used to mask treatments.

Treatment

Patients were randomly assigned in a 1:1 ratio to receive 1·5 g intravenous ceftolozane-tazobactam every 8 h or 750 mg intravenous levofloxacin once daily, both for 7 days. Creatinine clearance was measured at baseline to exclude patients with severe renal failure from entering the study and to assess whether dose adjustment of the study drug was required on the basis of renal function. Patients with severe renal failure (creatinine clearance less than 0·5 mL/s per m^2) were excluded because dosing recommendations for ceftolozane-tazobactam in this subgroup were not yet available. Doses were adjusted on the basis of creatinine clearance by a pharmacist who was aware of treatment allocation. Concomitant non-study antibiotics, except those with only Gram-positive activity, were not allowed. All patients received study drugs before the urine culture results were known, as they were not typically available until day 3. If the results showed resistance to one or both study drugs, investigators could modify treatment by stopping the study drug or by adding or replacing it with a non-study antibiotic, decided on the basis of the patient's clinical response.

Analysis populations

The modified intention-to-treat (MITT) and safety populations comprised all patients who received at least one dose of study drug. The microbiological

MITT population included all patients in the MITT population with growth of one or two uropathogens of at least 10^5 colony-forming units per mL in urine culture. Patients in the microbiological MITT population who adhered to the treatment protocol and had a clinical assessment and interpretable urine culture at the test-of-cure visit 5–9 days after the last dose of study drug comprised the per-protocol population. However, for patients who received concomitant active non-study antibiotics, those classified as having treatment failure were included in the per-protocol population, whereas those classified as responders were excluded.

Assessments

Complete physical examination and urine testing were mandatory before treatment was started. A qualifying baseline urine culture from the local laboratory was required to continue study treatment beyond day 3. Additional pathogen speciation and susceptibility testing were done at a central laboratory (ICON Laboratories, Farmingdale, NY, USA) with Clinical and Laboratory Standards Institute breakpoints for levofloxacin[18] and provisional breakpoints for ceftolozane-tazobactam (ie, susceptible, intermediate, and resistant, with the thresholds 8 mg/L or lower, 16 mg/L, and 32 mg/L or higher, respectively). *Enterobacteriaceae* spp organisms were classified as having an ESBL phenotype according to predefined criteria: minimum inhibitory concentration (MIC) 2 mg/L or higher for any cephalosporin, resistance to carbapenems, or MIC decrease of at least three dilutions when an antibiotic was combined with a β-lactamase inhibitor. Those identified before database lock were molecularly characterised at JMI Laboratories, North Liberty, IA, USA.

Clinical and microbiological outcomes were assessed at the test-of-cure visit. Clinical cure was defined as complete resolution, substantial improvement (ie, reduction in severity of all baseline signs and symptoms and worsening of none), or return to preinfection signs and symptoms of complicated lower-urinary-tract infections or pyelonephritis without the need for additional antibiotic therapy. Clinical failure was defined as the presence of one or more signs or symptoms of complicated lower-urinary-tract infections or pyelonephritis requiring additional antibiotics, or an adverse event leading to premature discontinuation of the study drug and the starting of additional antibiotic therapy. Microbiological eradication was defined as a test-of-cure urine culture with fewer than 10^4 colony-forming units per mL of the baseline uropathogen. Composite cure, the primary endpoint, was defined as achieving clinical cure and microbiological eradication of all baseline uropathogens. Patients with missing or indeterminate outcome data were classified as treatment failures in the microbiological MITT analysis and were excluded from the per-protocol analysis. Patients were reassessed in a late follow-up visit 21–42 days after the end of study treatment to assess sustained clinical cure. Safety was assessed by review of adverse events, vital signs, physical examination findings, and clinical laboratory results.

Statistical analysis

All statistical analyses were done on pooled data after database lock and before unmasking of the data, according to the prespecified statistical plan. Randomisation was stratified by study sites, but because the number of sites was large and the sample size at many was expected to be small, the primary analysis was prespecified to use geographic region as a stratification factor instead of individual study sites. The primary objective was to assess non-inferiority of ceftolozane-tazobactam compared with levofloxacin, based on the difference in composite cure rates at the test-of-cure visit in the microbiological MITT population. As a secondary objective the same endpoint was assessed in the per-protocol population. A pooled

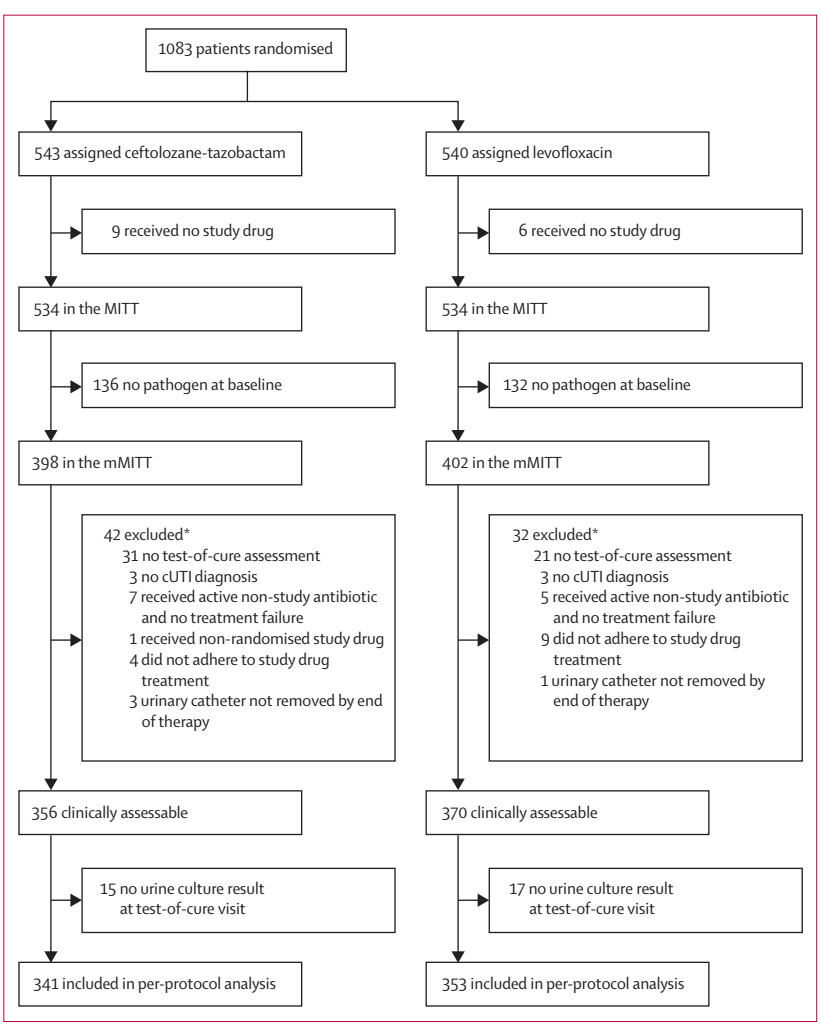

Figure 1: **Trial profile**
MITT=modified intention-to-treat population. mMITT=microbiological modified intention-to-treat population. cLUTI=complicated lower-urinary-tract infection. *Patients could have been excluded for more than one reason.

	Ceftolozane-tazobactam (n=398)	Levofloxacin (n=402)
Male	105 (26·4%)	103 (25·6%)
White ethnic origin	340 (85·4%)	346 (86·1%)
Age (years)	49·1 (19·7)	48·1 (20·2)
Age ≥65 years	100 (25·1%)	99 (24·6%)
Body-mass index (kg/m²)	25·5 (5·8)	26·1 (5·6)
Baseline creatinine clearance (mL/s per m²)		
Normal (≥1·3)	247 (62·1%)	274 (68·2%)
Mild renal impairment (>0·8 to <1·3)	116 (29·1%)	100 (24·9%)
Moderate renal impairment (≥0·5 to ≤0·8)	31 (7·8%)	27 (6·7%)
Severe renal impairment (<0·5)	3 (0·8%)	1 (0·2%)
Primary diagnosis		
Pyelonephritis	328 (82·4%)	328 (81·6%)
cLUTI	70 (17·6%)	74 (18·4%)
Antibiotics within 14 days before first dose*	14 (3·5%)	6 (1·5%)
Urinary catheter†	11 (2·8%)	10 (2·5%)
Bacteraemia	29 (7·3%)	33 (8·2%)
Diabetes	42 (10·6%)	40 (10·0%)
Hypertension	125 (31·4%)	119 (29·6%)

Data are number (%) or mean (SD). cLUTI=complicated lower-urinary-tract infections. *No antibiotics were permitted within 48 h before baseline urine culture. †Urinary catheter was removed before end of treatment in all but three patients in the ceftolozane-tazobactam group and one patient in the levofloxacin group.

Table 1: **Demographic and clinical baseline characteristics in the microbiological modified intention-to-treat population**

sample size of 800 patients in the microbiological MITT population, with an assumed composite cure rate of 74% in both study groups, ensured at least 90% power to show non-inferiority at a margin of 10%. The prespecified statistical criteria for the primary and secondary objective analyses was a two-sided 95% CI around the treatment difference with stratification by Newcombe minimum-risk weights.[19] These analyses were also done with a conservative 99% CI approach. Ceftolozane-tazobactam was declared non-inferior to levofloxacin if the lower bound of the two-sided 95% CI was greater than –10%. Although superiority was not specified as the secondary objective, a planned non-inferiority study can be tested for superiority without a need for type 1 error α correction.[20,21] We deemed that superiority was shown if the treatment difference was positive and the lower bound of the 95% CI around this difference was greater than zero. Other secondary endpoints of clinical cure, microbiological eradication, and composite cure in subgroups (primary diagnosis, age, presence of bacteraemia at baseline, susceptibility of the baseline uropathogen to levofloxacin and ceftolozane-tazobactam, and presence of ESBL-producing uropathogens) were analysed with 95% CI calculated by the Wilson score method.

Although the individual trials were not adequately powered to assess non-inferiority, the primary and secondary endpoints from each trial were summarised in a post-hoc exploratory analysis and the consistency of the treatment effect between the two protocols was tested at an α=0·05 significance level with the method proposed by Wiens and Heyse.[22] All statistical analyses were done with SAS (version 9.1.3 or higher).

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1083 patients were randomised into the study from multiple sites in Europe (n=812), South America (n=91), North America (n=50), and other geographic regions (n=130; figure 1, appendix). 15 (1·4%) did not provide consent or meet entry criteria. The safety population, therefore, included 1068 patients who received at least one dose of study drug. 1028 (94·9%) of randomised patients completed the study. 800 (73·9%) patients had a positive baseline urine culture and were included in the microbiological MITT population, of whom 106 (13·3%) were excluded from the per-protocol analysis (figure 1).

Baseline characteristics for the microbiological MITT population were similar in the two treatment groups (table 1). 656 (82·0%) of 800 patients had pyelonephritis at baseline, 274 (34·3%) had mild or moderate renal impairment, and 199 (24·9%) were aged 65 years or older. Of the 62 (7·8%) cases of bacteraemia at baseline, most were caused by *Escherichia coli* and were in patients with pyelonephritis.

776 (97·0%) of 800 patients in the microbiological MITT population had a monomicrobial infection, mostly with *E coli* (629 [78·6%] patients). Other frequently isolated Gram-negative uropathogens at baseline included *Klebsiella pneumoniae* (58 [7·3%]), *Proteus mirabilis* (24 [3·0%]), and *P aeruginosa* (23 [2·9%]). In the microbiological MITT population, 212 (26·5%) of 800 patients had levofloxacin-resistant uropathogens and 118 (14·8%) had ESBL-producing *Enterobacteriaceae* spp organisms isolated from the baseline urine culture.

Baseline susceptibility testing to study drugs showed that in the microbiological MITT population, 20 (2·7%) of 731 Gram-negative pathogens at baseline were resistant to ceftolozane-tazobactam, whereas 195 (26·7%) of 731 were resistant to levofloxacin (appendix). Of note, two (0·3%) of 594 of *E coli* isolates were resistant to ceftolozane-tazobactam, irrespective of ESBL phenotype, and 144 (24·2%) of 594 were resistant to levofloxacin.

Ceftolozane-tazobactam was non-inferior to levofloxacin for composite cure in the microbiological MITT and per-protocol populations (figure 2). Additionally, the results showed that ceftolozane-tazobactam was superior to levofloxacin for composite cure in both populations (figure 2). Sustained clinical cure rates in the clinically assessable population at late follow-up were 319 (96·4%)

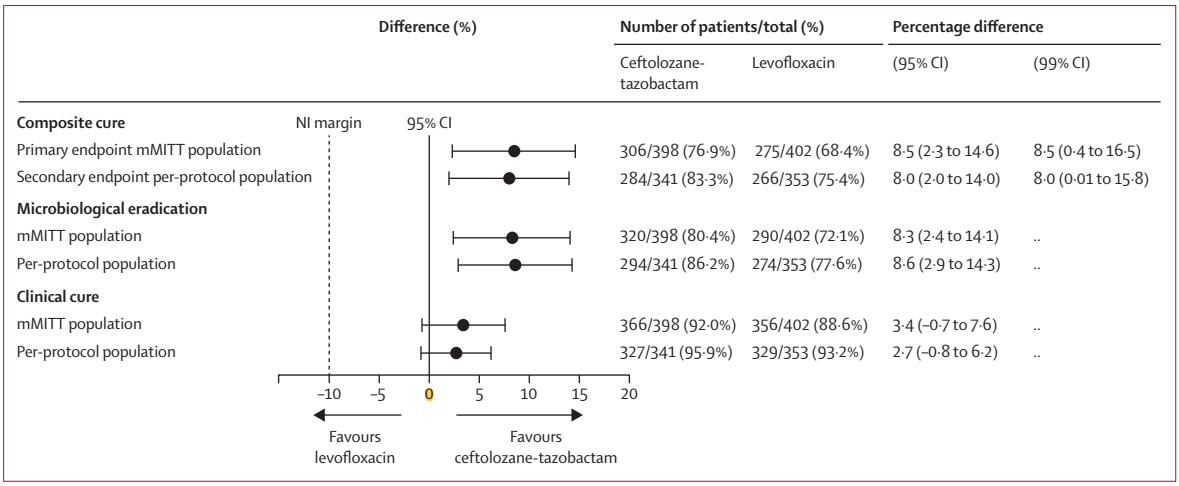

Figure 2: **Primary and secondary endpoints at the test-of-cure visit**
mMITT=microbiological modified intention-to-treat population. NI=non-inferiority.

of 331 and 314 (95·4%) of 329 in the ceftolozane-tazobactam and levofloxacin groups, respectively.

Ceftolozane-tazobactam was superior to levofloxacin for overall microbiological eradication in the microbiological MITT and per-protocol populations (figure 2). Ceftolozane-tazobactam was also superior to levofloxacin for microbiological eradication in patients in the per-protocol population who had *Enterobacteriaceae* spp infections at baseline and showed higher per-pathogen microbiological eradication in patients infected with *P aeruginosa* (table 2).

Subgroup analysis showed that the composite cure rates at the test-of-cure visit were significantly higher for ceftolozane-tazobactam than for levofloxacin among patients aged 65 years or older, those with complicated lower-urinary-tract infections, and those with levofloxacin-resistant or ESBL-producing uropathogens (figure 3). Clinical cure was seen in 90 (90·0%) of 100 patients in the ceftolozane-tazobactam group compared with 86 (76·8%) of 112 in the levofloxacin group with levofloxacin-resistant uropathogens (95% CI 3·1–22·9), and in 55 (90·2%) of 61 compared with 42 (73·7%) of 57 for patients with ESBL-producing uropathogens (95% CI 2·6–30·2). In all other subgroups composite cure rates were consistently higher in the ceftolozane-tazobactam group than in the levofloxacin group (figure 3).

The exploratory analysis of the primary and secondary endpoints in the individual trials supported non-inferiority of ceftolozane to levofloxacin. The differences in composite cure rates between treatments for the two individual trials were 2·5% (95% CI –6·3 to 11·2) and 14·5% (5·8 to 22·9) in the microbiological MITT population and 0·6% (–8·1 to 9·2) and 14·9% (6·6 to 23·1) in the per-protocol population. The prespecified interaction tests[22] showed no qualitative difference between trials.

The incidence of adverse events, including serious adverse events, was similar in the two treatment groups (table 3, appendix). Adverse events occurred in 185 (34·7%) of 533 and 184 (34·4%) of 535 patients in the ceftolozane-tazobactam and levofloxacin groups, respectively. The most frequent adverse events in both treatment groups were headache and gastrointestinal symptoms (table 3). Most adverse events were mild to moderate, and the incidence of treatment-limiting adverse events was less than 2% in each treatment group. Serious adverse events occurred in 15 (2·8%) of 533 and 18 (3·4%) of 535 patients in the ceftolozane-tazobactam and levofloxacin groups,

	Number of patients with a specific baseline pathogen/total number with baseline pathogens (%)		Percentage difference (95% CI)
	Ceftolozane-tazobactam	Levofloxacin	
Gram-negative aerobes			
All	287/323 (88·9%)	263/340 (77·4%)	11·5 (5·8 to 17·1)
Enterobacteriaceae spp	281/316 (88·9%)	255/327 (78·0%)	10·9 (5·2 to 16·6)
Escherichia coli	237/262 (90·5%)	226/284 (79·6%)	10·9 (4·9 to 16·8)
ESBL producers	27/36 (75·0%)	18/36 (50·0%)	NA
CTX-M-14/15*	20/27 (74·1%)	13/25 (52·0%)	NA
Klebsiella pneumoniae	21/25 (84·0%)	14/23 (60·9%)	23·1 (–2·1 to 45·4)
ESBL producers	7/10 (70·0%)	2/7 (28·6%)	NA
CTX-M-15*	5/8 (62·5%)	1/4 (25·0%)	NA
Proteus mirabilis	10/10 (100·0%)	8/11 (72·7%)	27·3 (–5·6 to 56·6)
Enterobacter cloacae	2/6 (33·3%)	6/7 (85·7%)	–52·4 (–78·8 to –0·3)
Pseudomonas aeruginosa	6/7 (85·7%)	7/12 (58·3%)	27·4 (–15·9 to 56·3)
Gram-positive aerobes			
All	8/21 (38·1%)	16/20 (80·0%)	–41·9 (–63·0 to –11·8)
Enterococcus faecalis	5/16 (31·3%)	12/16 (75·0%)	–43·8 (–66·4 to –9·2)
Enterococcus faecium	1/2 (50·0%)	3/3 (100·0%)	–50·0 (–90·6 to 19·3)
Staphylococcus aureus	3/4 (75·0%)	1/1 (100·0%)	–25·0 (–69·9 to 56·9)

ESBL=extended-spectrum β-lactamases. NA=not applicable, as CIs were not calculated. *Belong to a subset of extended-spectrum β-lactamase-producing pathogens.

Table 2: **Microbiological eradication at the test-of-cure visit by baseline pathogen in the per-protocol population**

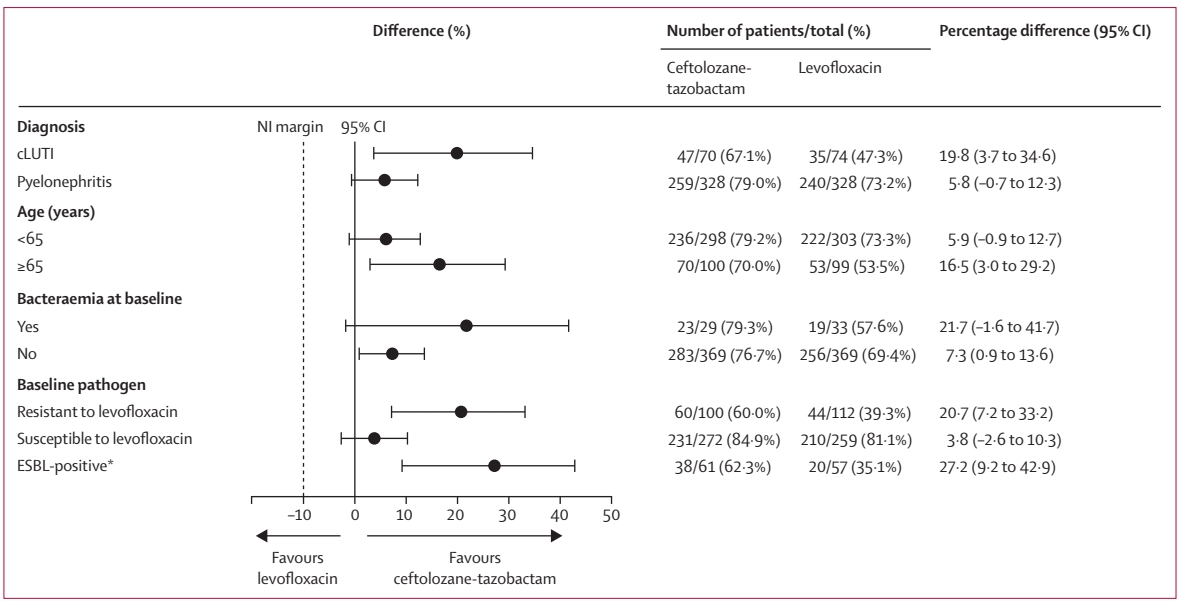

Figure 3: **Composite cure at test-of-cure visit, by subgroup, in the microbiological modified intention-to-treat population**
NI=non-inferiority. cLUTI=complicated lower-urinary-tract infection. ESBL=extended-spectrum β-lactamase. *Includes isolates of *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Enterobacter aerogenes*, and *Serratia marcescens*.

	Ceftolozane-tazobactam (n=533)	Levofloxacin (n=535)*
Headache	31 (5·8%)	26 (4·9%)
Constipation	21 (3·9%)	17 (3·2%)
Nausea	15 (2·8%)	9 (1·7%)
Diarrhoea	10 (1·9%)	23 (4·3%)
Upper abdominal pain	7 (1·3%)	6 (1·1%)
Vomiting	6 (1·1%)	6 (1·1%)
Hypertension	16 (3·0%)	7 (1·3%)
Pyrexia	8 (1·5%)	4 (0·7%)
Urinary-tract infection	9 (1·7%)	9 (1·7%)
Insomnia	7 (1·3%)	14 (2·6%)
Dizziness	6 (1·1%)	1 (0·2%)
Myalgia	6 (1·1%)	4 (0·7%)
Arthralgia	1 (0·2%)	6 (1·1%)
Increased alanine aminotransferase concentration	9 (1·7%)	5 (0·9%)
Increased aspartate aminotransferase concentration	9 (1·7%)	5 (0·9%)

Terms defined according to the Medical Dictionary for Regulatory Activity (version 14.1). *One patient randomised to ceftolozane-tazobactam actually received levofloxacin and was included in the levofloxacin group for all safety analyses.

Table 3: **Adverse events occurring in 1% or more of patients in either treatment group**

respectively (appendix). Two serious adverse events (*Clostridium difficile* infection) in the ceftolozane-tazobactam group were deemed to be related to study treatment. These two patients recovered by the time of late follow-up. One death, which was due to bladder cancer, occurred in the ceftolozane-tazobactam group but was deemed to be unrelated to study treatment. The incidence of adverse events related to alanine aminotransferase and aspartate aminotransferase concentrations was low and similar in the two treatment groups (table 3). In all but two cases (one in each group) they had returned to baseline values by the end of study. No laboratory abnormality resulted in an adverse event that led to premature discontinuation of study drug.

Discussion

Complicated urinary-tract infections are common health-care-associated infections with substantial antibiotic resistance.[4,23] We compared ceftolozane-tazobactam, a novel cephalosporin and β-lactamase-inhibitor combination, with a widely used fluoroquinolone recommended in clinical guidelines to treat such infections.[3,13] Our findings support the need to develop new effective antibiotics to combat the increasing resistance to antimicrobial agents, inadequate treatment, and the related poor clinical outcomes and substantial burden to health-care systems (panel).[3,5,7,9,24,25]

We chose the highest approved dose of levofloxacin as comparator for this trial, and treatment duration was extended beyond the labelled duration to ensure a clinically relevant regimen that reflects the difficulties related to fluoroquinolone resistance.[13–16,26] Only intravenous antibiotics were given in this trial, which probably led to selection of more seriously ill patients than if other routes of administration were used. Indeed, 82% of patients enrolled had pyelonephritis, which is associated with complications including organ failure and permanent renal impairment if not adequately treated.[27] The primary endpoint was based on the guidelines of the US Food and Drug Administration for clinical trials of complicated urinary-tract infections.[17] These guidelines suggested the use of the more stringent composite primary efficacy endpoint of clinical cure and microbiological eradication as well as the traditional endpoint of microbiological eradication.

In this trial, ceftolozane-tazobactam was superior to high-dose levofloxacin in a seriously ill population for composite cure rates, including in secondary analyses and in patients with resistant uropathogens. When assessed separately, both components of the composite cure endpoint favoured ceftolozane-tazobactam, which supports the primary outcome and the internal consistency of our results. Importantly, in view of the high and increasing prevalence of complicated urinary-tract infections due to ESBL-producing *E coli*,[12,28] ceftolozane-tazobactam achieved significantly higher eradication rates than levofloxacin in patients infected with *Enterobacteriaceae* spp, including ESBL-producing strains. *P aeruginosa* is an important pathogen in the spectrum of ceftolozane-tazobactam activity.[10] In vitro, ceftolozane-tazobactam has potent activity against *P aeruginosa*, including multidrug-resistant and extensively drug-resistant strains.[11,12] The findings for patients with *P aeruginosa* infections in this study were consistent with the overall outcomes. In view of the low incidence of *P aeruginosa* overall, however, we cannot draw any statistical conclusions. As reported elsewhere, enterococcal isolates are inherently resistant to cephalosporins and, as expected, we found low per-pathogen eradication rates against *Enterococcus faecalis* and *Enterococcus faecium* for ceftolozane-tazobactam in this study.

Overall, the trial enrolled a diverse population of patients with complicated lower-urinary-tract infections or pyelonephritis. The treatment difference in favour of ceftolozane-tazobactam was robust and consistent across different endpoints, analysis populations, subgroups, and disease subcategories. We found no data from registered trials of adult patients with complicated urinary-tract infections where an investigational antibiotic showed superior efficacy to an approved and widely used antibiotic.[26,29–33] Furthermore, despite the high proportion of patients in this study who had pyelonephritis, the microbiological eradication rates for ceftolozane-tazobactam were similar to those reported previously for other antibiotics widely used for complicated urinary-tract infections, which enrolled fewer numbers of seriously ill patients.[15,29,32,33]

The safety profile of ceftolozane-tazobactam was similar to that of levofloxacin in this study, and was generally consistent with profiles for the cephalosporin class of antibiotics.[30,34,35] The most frequent adverse events in the ceftolozane-tazobactam group, headache and nausea, are frequently associated with other antibiotics, were non-serious, and incidence was similar to that in the levofloxacin group. Antibiotics, specifically cephalosporins, are associated with a risk of developing *C difficile*-associated diarrhoea. The rate of *C difficile* infection in this study was low (<1%) and similar to the incidence reported with other cephalosporins.[34,35] Even though cases of *C difficile* infection occurred more frequently in the ceftolozane-tazobactam treatment group, diarrhoea was reported twice as often in the levofloxacin group.

Panel: Research in context

Systematic review

We identified references for this study by searching PubMed and Embase for articles published before July, 2014, with the search terms "complicated urinary tract infection" and "pyelonephritis" with "clinical trials", "treatment guidelines", "levofloxacin", and "antibiotic resistance." Results of this search suggested that complicated urinary-tract infections and pyelonephritis are caused mainly by Gram-negative pathogens and are important causes of morbidity and hospital admissions; resistance to antibacterials commonly used to treat complicated urinary-tract infections and pyelonephritis (eg, fluoroquinolone and β-lactam antibiotics) is an important global health-care concern; and, despite increasing resistance, fluoroquinolones (including high-dose levofloxacin), are recommended as first-line therapy in clinical guidelines and remain the most widely used antibacterials for treatment of complicated urinary-tract infections and pyelonephritis. These findings emphasise the need for novel antibacterials to treat complicated urinary-tract infections, including pyelonephritis. Ceftolozane-tazobactam has a number of promising pharmacological properties that make it a suitable candidate for clinical development in this setting.

Interpretation

In this large randomised, controlled, phase 3 trial of patients with complicated urinary-tract infections or pyelonephritis, with use of composite cure as the primary endpoint, we found that ceftolozane-tazobactam was non-inferior, and in fact superior, to the highest approved dose of levofloxacin given for 7 days. Our data are of clinical importance because they provide evidence-based proof of the declining reliability of empiric levofloxacin therapy in a large population of patients with complicated urinary-tract infections. As levofloxacin is recommended as the first-line therapy in various national and international treatment guidelines, these findings support the need for change to combat increasing antibiotic resistance. The data also suggest that ceftolozane-tazobactam will be a useful addition to the pharmacological armamentarium for treatment of complicated urinary-tract infections and pyelonephritis, especially those caused by difficult-to-treat pathogens that are levofloxacin resistant, produce extended-spectrum β-lactamases, or both.

Clinical guidelines recommend empiric fluoroquinolone therapy for complicated urinary-tract infections.[13,14] Our findings, however, provide evidence for the escalating prevalence of bacteria resistant to fluoroquinolones, producing ESBLs, or both,[24,25] and declining reliability of empiric levofloxacin therapy, even at the highest approved dose for 7 days. Ceftolozane-tazobactam was efficacious for the treatment of complicated lower-urinary-tract infections or pyelonephritis, including infections caused by difficult-to-treat uropathogens. This antibiotic, therefore, might add a therapeutic option for patients with potentially life-threatening infections.

Contributors

OU, JS, GY, and ROD contributed to the conception, design, or both, of the study. OU and JS were responsible for running the trial. FMW, OU, and JS enrolled patients and collected data. All authors contributed to data analysis, interpretation of the results, and preparation of the report, and all approved the final version.

Declaration of interests

FMW has served as a consultant to Cubist Pharmaceuticals. ROD previously provided limited consulting services to Cubist Pharmaceuticals that were not related to this study, and is currently involved in an investigator-initiated clinical trial of *Clostridium difficile*, funded originally by Optimer Pharmaceuticals and later Cubist Pharmaceuticals. OU, JS, and GY are employees of Cubist Pharmaceuticals.

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