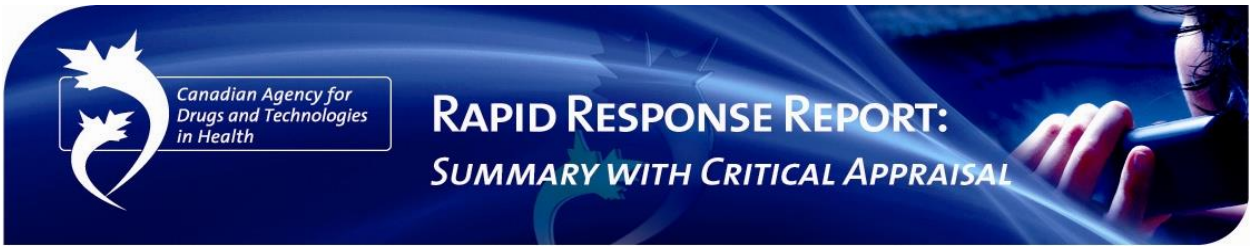

TITLE: Ceftolozane and Tazobactam for the Treatment of Bacterial Infections: A Review of Clinical Effectiveness, Cost-effectiveness, and Guidelines

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CONTEXT AND POLICY ISSUES

Antimicrobial resistance is a significant public health concern globally, and infections caused by drug-resistant Gram-negative bacteria are becoming increasingly common. For example, extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* that are resistant to common beta-lactam and non–beta-lactam antibiotics are responsible for up to one-third of hospital-acquired infections.[1] As antimicrobial resistance continues to be an issue across health care settings, guidelines for appropriate practices related to antibiotic prescribing and use are required. The prevalence of resistant pathogens has also encouraged the development of new treatment options to effectively combat them.

One recently developed antimicrobial therapy is the fixed-dose combination of ceftolozane (a novel cephalosporin) and tazobactam (a beta-lactamase inhibitor), marketed as Zerbaxa. It is provided as a lyophilized powder in a 1.5 g dose (1 g ceftolozane and 500 mg tazobactam) per vial for intravenous (IV) administration.[2] IV ceftolozane/tazobactam is indicated for the treatment of complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI), including pyelonephritis, caused by susceptible, primarily Gram-negative bacterial strains.[2] A cIAI is characterized by the spread of infection beyond the source organ (e.g., due to rupture or perforation) throughout the abdominal cavity to cause peritoneal inflammation.[3] A cUTI is an infection associated with structural or functional abnormalities in the genitourinary tract, such as indwelling catheters, stones or tumours in the urinary tract, or metabolic abnormalities involving the kidney.[4] Existing antimicrobial treatment options for cIAI include doripenem, meropenem, imipenem/cilastatin, ertapenem, tigecycline, and piperacillin/tazobactam, while antibiotics for cUTI include doripenem and levofloxacin.[1]

Health Canada issued a Notice of Compliance for Zerbaxa in September 2015 and the date of first sale was in January 2016.[5] Given the recent introduction of IV ceftolozane/tazobactam into clinical practice, evidence is required to support its broader use and to better understand its place in therapy relative to existing antimicrobial treatment options. The purpose of this report is

to evaluate the clinical effectiveness, cost-effectiveness, and evidence-based guidelines for the use of ceftolozane/tazobactam for patients with bacterial infections.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of ceftolozane and tazobactam for the treatment of bacterial infections in hospitalized patients?

2. What is the cost-effectiveness of ceftolozane and tazobactam for the treatment of bacterial infections in hospitalized patients?

3. What are the evidence-based guidelines regarding the use of ceftolozane and tazobactam for the treatment of bacterial infections in hospitalized patients?

KEY FINDINGS

Two high-quality randomized controlled trials and two associated subgroup analyses were identified regarding the clinical effectiveness of IV ceftolozane/tazobactam for the treatment of bacterial infections in hospitalized adult patients. One phase III clinical trial showed that IV ceftolozane/tazobactam plus metronidazole was non-inferior to IV meropenem for the treatment of complicated intra-abdominal infections, and subgroup analyses suggested that these results were consistent for patients with and without *P. aeruginosa*-related infection at baseline. A second clinical trial demonstrated that ceftolozane/tazobactam was statistically non-inferior and superior to IV levofloxacin for the treatment of complicated urinary tract infections, including pyelonephritis; the subgroup analysis showed that this effect was more pronounced in the subset of patients with levofloxacin-resistant pathogens at baseline. In both trials, the safety profiles of ceftolozane/tazobactam and its comparator were similar. The authors concluded that ceftolozane/tazobactam is a good antimicrobial option for the treatment of adults with complicated intra-abdominal infections, pyelonephritis, and complicated lower urinary tract infections, including for cases when antimicrobial-resistant pathogens are implicated. The generalizability of findings to a larger patient population with different patient characteristics from those included in the studies (e.g., patients with severe renal impairment, high-risk of mortality, elderly patients) may be limited. The subgroup analyses were limited by their sample sizes that were likely not sufficiently powered to show a true difference between groups and by the lack of randomization, which may have contributed to confounding.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and October 4, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Hospitalized patients with bacterial infections
Intervention	Ceftolozane/tazobactam (Zerbaxa) with or without other drugs
Comparator	Alternative antibiotic regimens (e.g., piperacillin and tazobactam, meropenem, levofloxacin)
Outcomes	Q1: Benefits and harms (e.g., successful treatment of infection, length of stay, adverse events) Q2: Cost-effectiveness outcomes (e.g., cost per QALY) Q3: Guidelines for use of ceftolozane and tazobactam (including place in therapy)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

QALY = quality-adjusted life year.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included randomized controlled trials were critically appraised using the Downs and Black checklist.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 99 citations were identified in the literature search. Following screening of titles and abstracts, 93 citations were excluded and six potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, six publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Detailed characteristics of included studies are provided in Appendix 2.

Study Design

Two double-blind, non-inferiority phase III RCTs, ASPECT-cIAI[7] and ASPECT-cUTI,[8] and two non-randomized subgroup analyses[9,10] of those RCTs were identified. The RCT samples sizes were calculated to provide at least 90% power to detect non-inferiority at a margin of 10%.

Country of Origin

Both RCTs were multicentre trials. ASPECT-cIAI was conducted in 196 study sites worldwide.[7] ASPECT-cUTI was conducted in multiple sites in Europe, South America, North America, and other regions.[8]

Patient Population

ASPECT-cIAI included adults with clinical evidence of complicated intra-abdominal infections (cIAI).[7] Microbiological confirmation of cIAI in an intra-abdominal specimen sampled within 24 hours of enrollment was required for inclusion in the study. Patients were excluded if they had inadequate source control of the infection, if they underwent staged abdominal repair in which the fascia was not closed, or if they were considered unlikely to survive the four to five week study period. The published subgroup analysis of ASPECT-cIAI by Miller et al.[9] evaluated the subgroup of patients with and without *Pseudomonas aeruginosa*-related cIAI at baseline.

ASPECT-cUTI[8] included adults with pyuria and pyelonephritis or complicated lower-urinary-tract-infection (cLUTI). Patients were considered to have pyelonephritis if they had at least two of the following symptoms: fever (with rigors, chills, or warmth), flank pain, regional tenderness on physical examination, nausea, or vomiting. cLUTI included those symptoms and also required the presence of suprapubic pain, painful, frequent, or urgent urination, plus at least one complicating factor. Eligible complicating factors included male sex with a history of urinary retention, the presence of a temporary indwelling urinary catheter or obstructive uropathy (if scheduled to be removed or surgically managed before the end of treatment), or any functional or anatomical urogenital abnormality that affected bladder voiding. Patients were excluded if they had an intractable UTI at baseline that investigators anticipated would require more than seven days of therapy, suspected or confirmed prostatitis, perinephric or intrarenal abscess, or permanent obstruction of the urinary tract. The subgroup analysis by Huntington et al.[10] evaluated the subgroup of patients with at least one levofloxacin-resistant uropathogen at baseline.

Patients in both RCTs were excluded if they received antimicrobial treatment for the current infection within 24 hours[7] or 48 hours[8] of the study baseline sample confirming infection, had concomitant infections that required additional antimicrobial therapy during the study (unless the antimicrobial had Gram-positive activity only), if they had a rapidly progressing or immediately life-threatening disease, or if they had severe renal function impairment (creatinine clearance < 30 mL/minute), as dosing recommendations for ceftolozane/tazobactam were not available for this population.[7,8]

Interventions and Comparators

The intervention in both RCTs[7,8] was the fixed-dose combination of IV ceftolozane/tazobactam 1.5 g every eight hours (1 g ceftolozane, 500 mg tazobactam); ASPECT-cIAI combined this with 500 mg metronidazole.[7] Metronidazole can be offered in combination with cephalosporins for

the treatment of cIAI.[11] According to the product monograph and the Health Canada Summary Basis of Decision for ceftolozane/tazobactam, the addition of metronidazole is specific to the cIAI indication to provide adequate anaerobic coverage.[2,5] The comparators were 1 g IV meropenem plus placebo every eight hours in ASPECT-cIAI[7] or 750 mg IV levofloxacin once daily in ASPECT c-UTI.[8] For ASPECT-cIAI patients with moderate renal impairment, the ceftolozane/tazobactam dose was reduced to 750 mg administered once every eight hours.[7] Ceftolozane/tazobactam dosing could be also modified during the ASPECT-cUTI study by a pharmacist according to the patient's creatinine clearance rate; however, no further details regarding the method of dose adjustment were provided.[8]

Treatment duration was four to ten days in ASPECT-cIAI, with the possibility of treatment extension to 14 days in patients with multiple abscesses, non–appendix-related peritonitis, failure of prior antimicrobial therapy, or hospital-acquired infection.[7] IV antimicrobial treatment was provided for seven days in ASPECT-cUTI.[8]

Outcomes

Primary outcomes were measured at the test-of-cure visit, which was 24 to 32 days after the start of treatment in ASPECT-cIAI[7] and five to nine days after completion of therapy in ASPECT-cUTI.[8]

The primary outcome in ASPECT-cIAI was clinical cure, described as complete resolution of infection, or significant enough improvement in signs and symptoms that no further intervention was required. Rate of clinical failure was also reported, defined as death from cIAI before the test-of-cure visit, requirement for additional antimicrobial therapy, or surgical site infection.[7] Results unavailable for any reason were classified as indeterminate and treated as failures in the microbiological intention-to-treat (ITT) population and excluded from the microbiologically evaluable (ME) population. The subgroup analysis evaluated the rate of clinical cure in patients in each treatment group with and without *P. aeruginosa* at baseline.[9]

The primary outcome in ASPECT-cUTI was a composite outcome of clinical cure (as described for ASPECT-cIAI) and microbiological eradication (test-of-cure urine culture with $< 10^4$ colony forming units per mL).[8] Secondary outcomes were individual rates of clinical cure and microbiological eradication. Clinical failures were defined as the presence of at least one sign or symptom of pyelonephritis or cLUTI requiring additional antimicrobial therapy, or the occurrence of an adverse event requiring study drug discontinuation and additional antibiotics. Indeterminate results and clinical failures were handled as described for ASPECT-cIAI. The subgroup analysis reported the same individual and composite outcomes for patients with levofloxacin-resistant uropathogens at baseline.[10]

Analysis Populations

Each included study evaluated effectiveness outcomes in a modified ITT population and a per-protocol (PP) population. Adverse events were also reported for the safety populations in the main RCT publications.[7,8]

ASPECT-cIAI analyzed clinical cure and failure rates in the microbiological ITT and ME populations. Patients could be enrolled in the study and randomized before a diagnosis of cIAI was confirmed, so the the microbiological ITT population referred to all randomized patients with at least one pathogen detected in the intra-abdominal sample taken at baseline, regardless of

the susceptibility of that pathogen to the study drug. Outcomes were also evaluated in the ME population, defined as all randomized patients who met the protocol-specific criteria regarding the definition of cIAI, amount of study drug received, timing of test-of-cure visit, otherwise adhered to trial procedures, and who had at least one pathogen identified at baseline that was susceptible to study drug.[7] The subgroup analysis for this study was conducted on the ME population.[9]

ASPECT-cUTI performed analyses in the microbiological modified ITT population and the PP population. The microbiological modified ITT population was defined as all randomized patients who had a positive urine culture at baseline and received at least one dose of study drug. The PP population was defined as the subset of patients in the modified microbiological ITT population who adhered to the treatment protocol and had a clinical assessment and an interpretable urine culture at the test-of-cure visit.[8] The subgroup analysis was also performed for both of these populations.[10]

Summary of Critical Appraisal

A detailed summary of the critical appraisal of each included study is provided in Appendix 3.

Overall, the studies were well designed and of high quality. Both RCTs[7,8] clearly reported the methods, including descriptions of the study objectives, patient inclusion and exclusion criteria, interventions, comparators, and outcomes. Both subgroup analysis publications[9,10] referred to the parent RCT for further description of the methods. Baseline characteristics including patient demographics, diagnoses, renal function, disease characteristics, and details of previous treatment were provided. ASPECT-cIAI[7] provided the baseline pathogen distribution between study groups, while ASPECT-cUTI[8] reported the proportion of all patients with each bacterium identified at baseline but did not describe their distributions in each treatment group. The impact of specific pathogens and antimicrobial resistance were evaluated in subsequent subgroup analyses.[9,10] Simple outcome data were provided for each analysis population, including numerators and denominators for each proportion reported. Findings were presented with 95% confidence intervals to describe the random variability in the data in all studies but the ASPECT-cIAI subgroup analysis.[9] Common adverse events (occurring in at least 1%[8] or 2%[7] of either treatment group) were reported in the main RCT publications. Reasons for exclusion from the per-protocol or microbiologically evaluable analyses were listed in ASPECT-cUTI[8] but were not clearly described in ASPECT-cIAI[7] or its subgroup analysis.[9]

The main limitations for both RCTs were related to their external validity; in both cases, the patients recruited for these studies may not be representative of all patients with cIAI[7] or cUTI.[8] For example, patients unlikely to survive the study period were excluded from ASPECT-cIAI, and disease severity was assessed at baseline using the Acute Physiology and Chronic Health Evaluation (APACHE) II tool, which is a measure for clinical status and in-hospital mortality risk typically applied to patients in intensive care units. Possible scores range from 0 to 71 (higher scores indicating a higher risk of death).[12] Approximately 97% of study patients had APACHE II scores of 15 or lower,[7] suggesting a low risk of mortality, which may not reflect the true risk of mortality in the larger population of patients with cIAI. In ASPECT-cUTI, the majority of patients recruited were females under the age of 65.[8] This may not be representative of a true patient population for cUTI, which can occur in men and women of any age.[4] Furthermore, male UTIs are usually considered complicated,[4] so the underrepresentation of men in this study may be concerning. The number of patients invited to participate in the studies were not reported, making it unclear whether those who agreed to participate were representative of the source

population. Both subgroup analyses were subject to the same patient recruitment and selection limitations as the parent RCTs. Eligible patients required IV antibiotics for their infections, so the hospital facilities and staff that were a part of the studies were representative of the treatment these patients would normally receive.

Potential biases were minimized in both RCTs[7,8] by randomizing the patients to treatment groups and blinding patients and outcome assessors to the group assignments; however, allocation concealment methods were not reported in one RCT.[7] Other strengths of the RCTs included recruiting all patients at each site from the same source populations at the same time, and measuring clearly defined outcomes at the test-of-cure visit with a set timeframe in both groups.[7,8] The non-inferiority margin for both trials was pre-specified as 10%; however, no clinical justification for the choice of this margin was provided. Both trials followed the recommended approach for non-inferiority trials by analyzing and reporting findings for both an ITT population (which accounted for drop-outs and treatment failures) and a PP population (which tends to show differences between treatment groups, if they exist).[7,8] Power calculations were performed and the final sample sizes in the ITT populations met the pre-specified thresholds to demonstrate non-inferiority of ceftolozane/tazobactam with 90% power at the defined non-inferiority margin.[7,8]

The subgroup analyses had some methodological limitations as it was unclear in ASPECT-cIAI whether it was planned a priori,[9] and the subgroups were not incorporated as stratification factors at baseline; neither of the subgroup analyses were randomized.[9,10] As a result, some baseline characteristics, such as age,[9,10] sex,[10] and diagnosis[10] were not evenly distributed between subgroups, and the impact of these or other potential confounders was not discussed. Both subgroup analyses described baseline characteristics in their respective ITT populations and evaluated clinical outcomes in the ME or PP populations. However, both analyses reported population sizes that were discrepant from those reported in the main RCT; the ASPECT-cIAI subgroup analysis reported a larger ME population (n = 652)[9] than the main RCT publication (n = 596),[7] and the microbiological modified ITT population of the ASPECT-cUTI subgroup analysis had 57 fewer patients than were reported in the main RCT. In both cases, no explanation was provided for the discrepancy in population sizes. Appropriate statistical tests were used to compare these differences at baseline and after treatment. As the parent RCTs were powered for the primary outcomes in the entire study population, it is unlikely that they were sufficiently powered for further subgroup analyses.

Summary of Findings

Detailed study findings are provided in Appendix 4.

What is the clinical effectiveness of ceftolozane and tazobactam for the treatment of bacterial infections in hospitalized patients?

Complicated Intra-abdominal Infections (cIAI)

One RCT, ASPECT-cIAI,[7] and one subgroup analysis of this RCT[9] were identified regarding the clinical effectiveness of IV ceftolozane/tazobactam plus metronidazole compared with IV meropenem for the treatment of cIAI. A total of 806 patients were included in the microbiological ITT population; the majority of patients were male (58%), white (94%), and between the ages of 18 and 64 (77%). The most common site of infection origin was the appendix in 48% of patients, leading to the most common diagnosis of appendiceal perforation or abscess in 47% of patients

in the microbiological ITT population. Approximately 30% of all patients had mild or moderate renal impairment, and 87% of patients had a baseline APACHE II score under 10, with a mean score of 6.2 (standard deviation [SD] 4.2) in the ceftolozane/tazobactam plus metronidazole group and 6.0 (SD 4.1) in the meropenem group, indicating a generally low risk of mortality at baseline in both groups. The distribution of patient characteristics, including the pathogens identified at baseline, was similar between treatment groups in the microbiological ITT population.[7]

ASPECT-cIAI found that ceftolozane/tazobactam plus metronidazole and meropenem groups demonstrated high clinical cure rates at the test-of cure visit in both the microbiological ITT population (83.0% and 87.3%, respectively) and the ME population (94.2% and 94.7%, respectively). Furthermore, ceftolozane/tazobactam and metronidazole were statistically non-inferior to meropenem for this primary outcome in both analysis populations. Clinical cure rates continued to increase in both treatment groups in the microbiological ITT population from the test-of-cure visit to the end-of-treatment follow-up visit 38 to 45 days after start of therapy (89.2% for ceftolozane/tazobactam plus metronidazole and 92.3% for meropenem); the difference between groups was not statistically significant. Clinical cure rates were lower for both treatments in certain subgroups when compared with the entire ME population, including elderly patients, those with APACHE II scores of 10 or greater, moderate renal impairment, and small bowel or colon infections. The power calculations for the primary outcomes assumed a clinical cure rate of 75% in both arms; this clinical cure rate was surpassed for both treatment arms in each of these subgroups except for patients with moderate renal impairment (72.7% [8/11] with ceftolozane/tazobactam plus metronidazole and 71.4% [5/7] with meropenem). Clinical cure rates were comparable between treatment groups at the test-of-cure visit for the subset of evaluable patients with ESBL-producing *Enterobacteriaceae.* The rate of adverse events overall and the types of adverse events reported were similar between treatment groups, and most events were mild to moderate in severity. The most frequent adverse events in both treatment groups were nausea, diarrhea, vomiting, and pyrexia.[7]

The subgroup analysis by Miller et al.[9] evaluated clinical cure rates in patients in the ME population with and without *P. aeruginosa* infection at baseline. *P. aeruginosa* was reported to be the third most common pathogen in ASPECT-cIAI, identified in 72 of 806 patients (8.9%) in the microbiological ITT population.[7] Clinical cure rates in the ME population were high in both treatment groups, regardless of *P. aeruginosa* status at baseline, and ranged from 93.0% to 100%. The statistical significance of the difference between groups was not assessed.

Pyelonephritis and Complicated Lower Urinary Tract Infections (cLUTI)

One RCT, ASPECT-cUTI,[8] and one subgroup analysis of this RCT[10] were identified regarding the clinical effectiveness of IV ceftolozane/tazobactam compared with IV levofloxacin for the treatment of pyelonephritis or cLUTI. A total of 800 patients were included in the microbiological modified ITT population; the majority of patients were female (74%), white (86%), and between the ages of 18 and 64 (75%). Of the two possible primary diagnoses, 82% of patients in the microbiological ITT population had pyelonephritis, while the remaining 18% of patients were diagnosed with cLUTI. Approximately 34% of all patients had mild or moderate renal impairment. The reported distributions of patient characteristics were similar between treatment groups in the microbiological ITT population; however, the distribution of baseline pathogens between groups were not described.[8]

ASPECT-cUTI found that ceftolozane/tazobactam demonstrated statistical non-inferiority and superiority to levofloxacin for composite cure rates at the test-of cure visit in both the microbiological ITT population (76.9% versus 68.4%) and the PP population (83.3% versus 75.4%). In addition, ceftolozane/tazobactam was shown to be non-inferior to levofloxacin for clinical cure rates and superior to levofloxacin for microbiological eradication rates in both analysis populations. Clinical cure rates were high in both treatment groups in the clinically assessable patients at the late follow-up visit 21 to 42 days after the end of therapy (n = 660; 96.4% for ceftolozane/tazobactam and 95.4% for levofloxacin). The rate of adverse events overall and the types of adverse events reported were similar between treatment groups, and most events were mild to moderate in severity. The most frequent adverse events in both treatment groups were headache, constipation, nausea, and diarrhea.[8]

The subgroup analysis by Huntington et al.[10] evaluated clinical cure rates in patients in the ME population with and without levofloxacin-resistant pathogens. Baseline susceptibility testing showed that 2.7% of Gram-negative pathogens were resistant to ceftolozane/tazobactam, while 26.7% of Gram-negative pathogens were resistant to levofloxacin.[8] The subgroup analysis showed that among patients with levofloxacin-resistant pathogens at baseline, the composite cure rate at the test-of-cure visit was significantly higher in the ceftolozane/tazobactam group than the levofloxacin group in both analysis populations (60.0% versus 39.3% in the microbiological ITT and 64.0% versus 43.4% in the PP population). Similarly, the clinical cure rates and microbiological eradication rates were significantly higher with ceftolozane/tazobactam than levofloxacin in the microbiological ITT population.[10] These findings suggest that the results showing superiority of ceftolozane/tazobactam in the main RCT were at least partially driven by the inclusion of patients with levofloxacin-resistant pathogens who would be less likely to respond to the comparator treatment. However, as composite cure rates were lower in this levofloxacin-resistant subgroup compared with the entire study population for either treatment group, the authors suggested that levofloxacin-resistance is an independent predictor of treatment failure due to patient characteristics including but not limited to drug-specific pathogen resistance. The clinical outcomes for the levofloxacin-susceptible subgroup were not presented.

What is the cost-effectiveness of ceftolozane and tazobactam for the treatment of bacterial infections in hospitalized patients?

No relevant evidence regarding the cost-effectiveness of ceftolozane and tazobactam for the treatment of bacterial infections was identified; therefore, no summary can be provided.

What are the evidence-based guidelines regarding the use of ceftolozane and tazobactam for the treatment of bacterial infections in hospitalized patients?

No relevant evidence-based guidelines regarding the use ceftolozane and tazobactam for the treatment of bacterial infections was identified; therefore, no summary can be provided.

Limitations

This review was limited by the lack of evidence identified to address the research questions on the cost-effectiveness and guidelines regarding the use of IV ceftolozane/tazobactam. This is likely because this drug combination is relatively new; it was issued a Notice of Compliance by Health Canada in September 2015.[5] This decision was based on a review of two pivotal clinical trials, ASPECT-cIAI[7] and ASPECT-cUTI,[8] which, along with their separately published subgroup

analyses,[9,10] were the only relevant studies identified for this report. No studies that evaluated other antimicrobial comparisons of interest (e.g., against piperacillin/tazobactam) were identified for this review.

The generalizability of the RCT findings was somewhat limited by the patient populations studied. For example, cIAI-related mortality rates can be significant, ranging from 5% for patients with appendicitis up to 50% for patients with large bowel perforation;[11] however, the majority of patients included in ASPECT-cIAI were at a low risk of mortality. In ASPECT-cUTI, the primary and secondary outcomes were presented for the total study population but more than 80% of patients had a diagnosis of pyelonephritis, suggesting that the results were primarily driven by this group and the observed treatment outcomes may not be generalizable to patients with cLUTI. ASPECT-cUTI also excluded patients with permanent indwelling catheters; therefore, the effectiveness of ceftolozane/tazobactam is uncertain in patients with this common risk factor for cUTI. The majority of patients included in both trials were under the age of 65 (77% in ASPECT-cIAI[7] and 75% in ASPECT-cUTI[8]), so generalizability of findings is also limited for elderly patients. Ceftolozane/tazobactam has not been studied in pregnant or nursing women, and patients with severe renal impairment were excluded from both RCTs; therefore, the safety and effectiveness of this antimicrobial combination in these patient populations is unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Two high-quality RCTs[7,8] and their subgroup analyses[9,10] were identified regarding the clinical effectiveness of IV ceftolozane/tazobactam alone[8,10] or in combination with metronidazole[7,9] for the treatment of bacterial infections in hospitalized adult patients. ASPECT-cIAI showed that IV ceftolozane/tazobactam with metronidazole was non-inferior to IV meropenem for the treatment of cIAI,[7] and subgroup analyses suggested that these results were consistent for patients with and without *P. aeruginosa*-related infection at baseline.[9] ASPECT-cUTI showed that ceftolozane/tazobactam was statistically non-inferior and superior to IV levofloxacin for the treatment of cUTI,[8] and subgroup analyses demonstrated that this effect was more pronounced in the subset of patients with levofloxacin-resistant pathogens at baseline.[10] In both trials, the safety profiles of ceftolozane/tazobactam and its comparator were similar. The authors concluded that ceftolozane/tazobactam is a good antimicrobial option for the treatment of adults with cIAI, pyelonephritis, and cLUTI, including for cases when antimicrobial-resistant pathogens are implicated. The generalizability of findings to a larger patient population with different patient characteristics from those included in the studies (e.g., patients with severe renal impairment, high-risk of mortality, elderly patients) may be limited. The subgroup analyses were limited by their sample sizes that were likely not sufficiently powered to show a true difference between groups and by the lack of randomization, which may have contributed to confounding.

The National Institute for Health and Care Excellence (NICE) conducted evidence reviews of ASPECT-cIAI and ASPECT-cUTI and concluded that IV ceftolozane/tazobactam is an option for the treatment of cIAI and acute pyelonephritis in some adult patients, in cases of bacterial resistance to or contraindications to other first-line empiric therapy options and susceptibility to ceftolozane/tazobactam.[13,14] NICE also commented that despite the licensed indication to treat cLUTI, there are limited data to support the clinical efficacy of ceftolozane/tazobactam for this indication, given the smaller number of patients with cLUTI than pyelonephritis in the mixed study population.[13] While NICE did not perform a cost-effectiveness analysis, unit costs and costs per seven day course of therapy were described for ceftolozane/tazobactam and relevant antimicrobial treatment comparators; this indicated that the acquisition price of

ceftolozane/tazobactam for the National Health Service exceeds that of other IV antibiotic options for both cIAI and cUTI. NICE suggested that determinations about place in therapy should be based on considerations of clinical effectiveness and safety, cost, individual patient characteristics, local guidelines and policies for antibiotic use and cIAI and cUTI management, as well as the principles of antimicrobial stewardship.[13,14]

Evidence-based guidelines regarding the place in therapy of ceftolozane/tazobactam were not identified for this report; however, Health Canada has approved the use of IV ceftolozane/tazobactam in adults for the treatment of cIAI (in combination with metronidazole) and cUTI, including pyelonephritis, when caused by specific strains of bacteria that are susceptible to this drug.[5] Known or highly suspected pathogen susceptibility is a main requirement for choosing ceftolozane/tazobactam, according to the Health Canada Summary Basis of Decision, and when direct susceptibility data (e.g., from cultures) are not available, Health Canada suggests considering local epidemiology and resistance patterns to inform treatment selections.[5]

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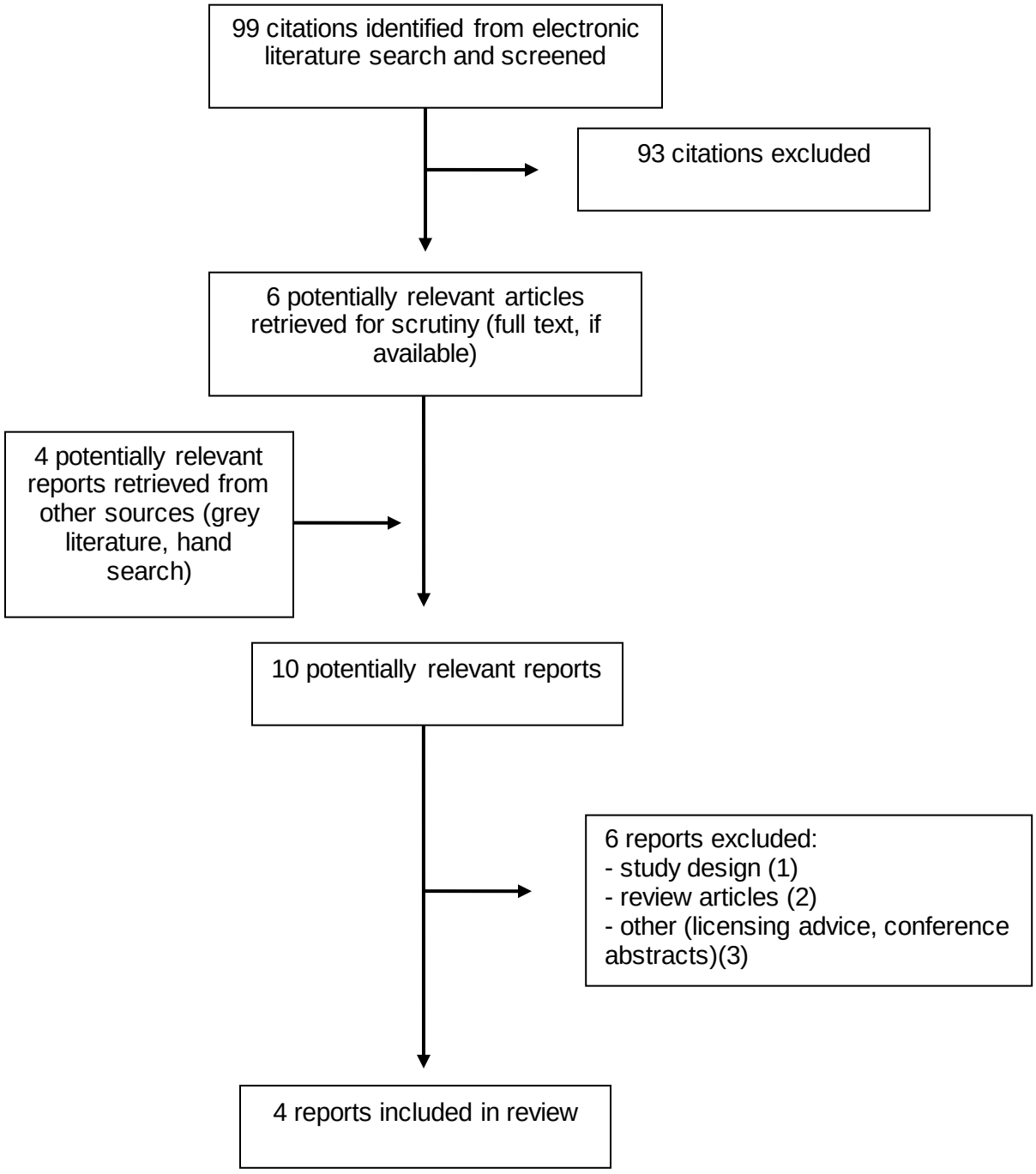
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Complicated Intra-abdominal Infections					
Miller 2016[9]	Non-randomized subgroup analysis of ASPECT-cIAI	Adults (≥ 18 years) with (n = 72) and without (n = 734) *Pseudomonas aeruginosa*-related cIAI at baseline	IV ceftolozane/tazobactam 1.5 g (1 g ceftolozane and 500 mg tazobactam) plus metronidazole 500 mg every 8 hours for 4 to 10–14[a] days Patients with creatinine clearance 30–50 mL/minute: IV ceftolozane/tazobactam 750 mg every 8 hours	IV meropenem 1 g plus placebo every 8 hours for 4 to 10–14[a] days Patients with creatinine clearance 30–50 mL/minute: IV meropenem 1 g every 12 hours	Clinical cure (complete resolution or significant improvement of signs and symptoms such that no further intervention is required) at TOC visit (24-32 days after start of treatment)
Solomkin 2015, ASPECT-cIAI[7]	Phase III non-inferiority RCT	Adults (≥ 18 years) with cIAI (n = 993) Exclusions: "cIAI managed by staged abdominal repair in which the fascia was not closed; low likelihood of adequate source control at surgery; creatinine clearance < 30 mL/minute; or use of systemic antimicrobial therapy for IAI for > 24 hours prior to the first dose of study drug (unless this treatment failed)"[b]	IV ceftolozane/tazobactam 1.5 g (1 g ceftolozane and 500 mg tazobactam) plus metronidazole 500 mg every 8 hours for 4 to 10–14[a] days Patients with creatinine clearance 30–50 mL/minute: IV ceftolozane/tazobactam 750 mg every 8 hours n = 487	IV meropenem 1 g plus placebo every 8 hours for 4 to 10–14[a] days Patients with creatinine clearance 30–50 mL/minute: IV meropenem 1 g every 12 hours n = 506	Clinical cure (complete resolution or significant improvement of signs and symptoms such that no further intervention is required); clinical failure (death from cIAI before TOC visit, requirement for additional antimicrobials, SSI) at TOC visit (24–32 days after start of treatment)

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Complicated Urinary Tract Infections					
Huntington 2016[10]	Non-randomized subgroup analysis of ASPECT-cUTI	Adults (≥ 18 years) with pyuria and cUTI or pyelonephritis, with (n = 212) or without (n = 531) levofloxacin-resistant pathogens at baseline	IV ceftolozane/tazobactam 1.5 g every 8 hours for 7 days Doses adjusted based on creatinine clearance rate by pharmacist aware of treatment allocation	IV levofloxacin 750 mg once daily for 7 days	Clinical cure, microbiological eradication (TOC urine culture with < 10^4 cfu/mL), or composite cure (both clinical and microbiological) at the TOC visit (5–9 days after end of treatment)
Wagenlehner 2015, ASPECT-cUTI[8]	Phase III non-inferiority RCT	Adults (≥ 18 years) with pyuria and cUTI or pyelonephritis (n = 1083) Exclusions: concomitant infections requiring treatment with Gram-negative antimicrobials, infections at baseline requiring > 7 days of treatment, use of non-study antimicrobials within 48 hours of urine collection and prior to study drug initiation, patients with severe renal failure (creatinine clearance rate < 0.5 mL/second per m^2)	IV ceftolozane/tazobactam 1.5 g every 8 hours for 7 days Doses adjusted based on creatinine clearance rate by pharmacist aware of treatment allocation n = 543	IV levofloxacin 750 mg once daily for 7 days n = 540	Primary composite outcome of clinical cure (complete resolution or significant improvement of signs and symptoms such that no further intervention is required) and microbiological eradication (TOC urine culture with < 10^4 cfu/mL) at TOC visit (5–9 days after end of treatment); secondary outcomes were clinical cure rate and microbiological eradication rate

AE = adverse event; ASPECT = Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam; cfu = colony forming units; cIAI = complicated intra-abdominal infections; cUTI = complicated urinary tract infections; IV = intravenous; SSI = surgical site infection; TOC = test-of-cure.

[a] Treatment could be continued up to 14 days in patients with any one of the following: multiple abscesses, non-appendix–related diffuse peritonitis, failure of prior antimicrobial therapy, or hospital-acquired infection.[7]

[b] Systemic antimicrobial treatment failure defined as "the need for additional intervention and persistent signs of ongoing infection with a positive culture of intra-abdominal abscess or peritonitis fluid, despite > 48 hours of prior antimicrobial therapy."[7]

APPENDIX 3: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black checklist[6]

Strengths	Limitations
Complicated Intra-abdominal Infections	
Miller 2016[9]	
• Clearly described study objectives (subgroup analysis) • Referred to parent trial publication (ASPECT-cIAI) which had clearly described inclusion and exclusion criteria, interventions, comparators, and outcomes in the methods • Baseline characteristics including potential confounders outlined for both population subgroups • Main findings clearly described • Study environment (in hospital) representative of the level of care most patients with cIAI would receive • Patients and outcome assessors were blinded to treatment allocation • Outcomes measured at the same time (test-of-cure visit with a standard time frame) for all patients • Compliance with the intervention was reliable • Main outcome measures were valid and reliable • Patients in both treatment groups were recruited from the same population, over the same period of time; subgroup analysis performed on this population	• No estimates of the random variability in the data provided • Adverse events not reported for this subgroup analysis • Patients excluded from the microbiologically evaluable (per-protocol) analysis not described • Subgroup analysis subject to the same patient recruitment and selection strategy limitations as the parent study (ASPECT cIAI) • Unclear whether this subgroup analysis was planned a priori • *P. aeruginosa* status not used as a stratification factor at randomization; this subgroup analysis was not randomized • Allocation concealment not described • Potential impact of confounders not addressed • Likely insufficient power to detect a difference between groups
Solomkin 2015, ASPECT-cIAI[7]	
• Clearly described study objectives, inclusion and exclusion criteria, interventions, comparators, and outcomes in the methods • Baseline characteristics including potential confounders outlined for both treatment groups • Main findings were clearly described • Confidence intervals provided to provide estimates of random variability in the data • Adverse events with frequency of at least 2% in any treatment group reported • Study environment (in hospital) representative of the level of care most patients needing IV antimicrobial therapy receive • Patients and outcome assessors were blinded • Outcomes measured at the same time (test-of-cure visit with a standard time frame) for both groups	• Reasons for patient loss to follow-up (assumed to be part of "protocol deviation" exclusions) not provided • Patients recruited (e.g., low-risk of mortality) may not be representative of all patients with cIAI • Unclear number of patients invited to participate • Unclear whether subgroup analyses were planned a priori • Allocation concealment not described

Table A2: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black checklist[6]	
Strengths	**Limitations**
• Appropriate statistical tests were used to assess the data • Compliance with the intervention was reliable • Main outcome measures were valid and reliable • Patients in both treatment groups were recruited from the same population, over the same period of time • Patients were randomized to treatment groups • Adequate adjustments for confounding made (ITT population analyzed for primary outcome) • Power calculation performed	
Complicated Urinary Tract Infections	
Huntington 2016[10]	
• Clearly described study objectives (subgroup analysis) • Referred to parent trial publication (ASPECT-cUTI) which had clearly described inclusion and exclusion criteria, interventions, comparators, and outcomes in the methods • Baseline characteristics including potential confounders outlined for both population subgroups • Main findings clearly described • Confidence intervals provided to provide estimates of random variability in the data • Study environment (in hospital) representative of the level of care most patients with cIAI would receive • Patients and outcome assessors were blinded to treatment allocation • Subgroup analysis was pre-specified • Outcomes measured at the same time (test-of-cure visit with a standard time frame) for all patients • Appropriate statistical tests were used to assess the data • Compliance with the intervention was reliable • Main outcome measures were valid and reliable • Patients in both treatment groups were recruited from the same population, over the same period of time; subgroup analysis performed on this population	• Adverse events not reported for this subgroup analysis • 57 patients from the modified microbiological ITT population excluded from subgroup analysis for unclear reasons • Subgroup analysis subject to the same patient recruitment and selection strategy limitations as the parent study (ASPECT cUTI) • Levofloxacin-resistance not used as a stratification factor at randomization; this subgroup analysis was not randomized • Potential impact of confounders not addressed • Subgroup analysis not prospectively powered
Wagenlehner 2015, ASPECT-cUTI[8]	
• Clearly described study objectives, inclusion and exclusion criteria, interventions, comparators, and outcomes in the methods	• Patients recruited (e.g., majority female, normal to mild renal function) may not be representative of all patients with cUTI

Table A2: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black checklist[6]

Strengths	Limitations
• Baseline characteristics including potential confounders outlined for both treatment groups • Main findings were clearly described • Confidence intervals provided to provide estimates of random variability in the data • Adverse events with frequency of at least 1% in any treatment group reported • Reasons for exclusion from the ITT populations and number of patients for each reason provided • Study environment (in hospital) representative of the level of care most patients needing IV antimicrobial therapy receive • Patients and outcome assessors were blinded • Outcomes measured at the same time (test-of-cure visit with a standard time frame) for both groups • Appropriate statistical tests were used to assess the data • Compliance with the intervention was reliable • Main outcome measures were valid and reliable • Patients in both treatment groups were recruited from the same population, over the same period of time • Patients were randomized to treatment groups and allocation concealment was described • Adequate adjustments for confounding made (ITT population analyzed for primary outcome) • Power calculation performed	• Unclear number of patients invited to participate • Unclear whether subgroup analyses were planned a priori

cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; IV = intravenous; ITT = intention-to-treat.

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A3: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Complicated Intra-abdominal Infections	
Solomkin 2015, ASPECT-cIAI[7]	

	Ceftolozane/ tazobactam plus metronidazole, n (%)	Meropenem, n (%)
microbiological ITT population[b] (n = 806)		
Clinical cure rate	323/389 (83.0)	364/417 (87.3)
Weighted difference between groups	–4.2% (95% CI –8.91% to 0.54%)	
Failure rate	32/389 (8.2)	34/417 (8.2)
Indeterminate	34/389 (8.7)	19/417 (4.6)
ME population[a] (n = 596)		
Clinical cure rate	259/275 (94.2)	304/321 (94.7)
Weighted difference between groups	–1.0% (95% CI –4.52% to 2.59%)	
Failure rate	16/275 (5.8)	17/321 (5.3)
Safety (n = 979)		
Any AE	212/482 (44.0)	212/497 (42.7)
Nausea	38/482 (7.9)	29/497 (5.8)
Diarrhea	30/482 (6.2)	25/497 (5.0)
Vomiting	16/482 (3.3)	20/497 (4.0)
Pyrexia	25/482 (5.2)	20/497 (4.0)

- Comparable clinical cure rates between treatment groups in patients with ESBL-producing Enterobacteriaceae (95.8% [23/24] with ceftolozane/tazobactam plus metronidazole and 88.5% [23/26] with meropenem)

"In conclusion, these results suggest that ceftolozane/tazobactam plus metronidazole is a potential alternative to the currently recommended antimicrobials for the treatment of cIAIs, especially when resistant Enterobacteriaceae or P. aeruginosa are suspected, such as in healthcare-associated infections." Page 1469

Miller 2016[9]

- Clinical cure rate at test-of-cure visit

	Ceftolozane/ tazobactam plus metronidazole, n (%)	Meropenem, n (%)
ME population[a]		
P. aeruginosa at baseline	26/26 (100)	27/29 (93.1)
No *P. aeruginosa* at baseline	262/281 (93.2)	294/316 (93.0)

"The ASPECT-cIAI findings suggest that ceftolozane/tazobactam will be an important addition to the available antibacterials used in the treatment of cIAIs, especially when P. aeruginosa is implicated." Page 4390

Table A3: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Complicated Urinary Tract Infections	
Wagenlehner 2015, ASPECT-cUTI[8]	

	Ceftolozane/ tazobactam, n (%)	Levofloxacin, n (%)
Microbiological modified ITT population[c] (n = 800)		
Composite cure rate	306/398 (76.9)	275/402 (68.4)
Weighted difference between groups	8.5% (95% CI 2.3% to 14.6%; 99% CI 0.4% to 16.5%)	
Clinical cure rate	366/398 (92.0)	356/402 (88.6)
Weighted difference between groups	3.4% (95% CI –0.7% to 7.6%)	
Microbiological eradication rate	320/398 (80.4)	290/402 (72.1)
Weighted difference between groups	8.3% (2.4% to 14.1%)	
Per-protocol population[d] (n = 694)		
Composite cure rate	384/341 (83.3)	266/353 (75.4)
Weighted difference between groups	8.0% (95% CI 2.0% to 14.0%; 99% CI 0.01% to 15.8%)	
Clinical cure rate	327/341 (95.9)	329/353 (93.2)
Weighted difference between groups	2.7% (95% CI –0.8% to 6.2%)	
Microbiological eradication rate	294/341 (86.2)	274/353 (77.6)
Weighted difference between groups	8.6% (95% CI 2.9% to 14.3%)	
Safety (n = 1068)		
Any AE	185/533 (34.7)	184/535 (34.4)
Headache	31/533 (5.8)	26/535 (4.9)
Constipation	21/533 (3.9)	17/535 (3.2)
Nausea	15/533 (2.8)	9/535 (1.7)
Diarrhea	10/533 (1.9)	23/535 (4.3)

Subgroup analyses – composite cure rates at test-of-cure visit

- Significantly higher for ceftolozane/tazobactam than for levofloxacin among:
  - patients ≥ 65 years (70.0% [70/100] vs. 53.5% [53/99]; difference: 16.5%, 95% CI 3.0% to 29.2%)
  - patients with cLUTI (67.1% [47/70] vs. 47.3% [35/74]; difference: 19.8%, 95% CI 3.7% to 34.6%)
  - patients with levofloxacin-resistant uropathogens (60.0% [60/100] vs. 39.3% [44/112]; difference: 20.7%, 95% CI 7.2% to 33.2%)
  - patients with ESBL-producing uropathogens (62.3% [38/61] vs. 35.1% [20/57]; difference: 27.2%, 95% CI 9.2% to 42.9%)
- No significant difference between ceftolozane/tazobactam and levofloxacin for patients < 65 years, with pyelonephritis, or with uropathogens susceptible to

"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." Page 1955

Table A3: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusions</th></tr>
<tr><td>levofloxacin</td><td></td></tr>
<tr><td>Huntington 2016[10]</td><td></td></tr>
<tr><td>

- Outcomes at test-of-cure visit in patients with levofloxacin-resistant pathogens at baseline

<table>
<tr><th></th><th>Ceftolozane/ tazobactam, n (%)</th><th>Levofloxacin, n (%)</th></tr>
<tr><td>Microbiological modified ITT population[c] (n = 212)</td><td></td><td></td></tr>
<tr><td>Composite cure rate</td><td>60/100 (60.0)</td><td>44/112 (39.3)</td></tr>
<tr><td>Difference between groups</td><td colspan="2">20.7% (95%CI 7.2% to 33.2%)</td></tr>
<tr><td>Clinical cure rate</td><td>90/100 (90.0)</td><td>86/112 (76.8)</td></tr>
<tr><td>Difference between groups</td><td colspan="2">13.2% (95% CI 3.1% to 22.9%)</td></tr>
<tr><td>Microbiological eradication rate</td><td>63/100 (63.0)</td><td>49/112 (43.8)</td></tr>
<tr><td>Difference between groups</td><td colspan="2">19.3% (95% CI 5.8 to 31.7)</td></tr>
<tr><td>Per-protocol population[d]</td><td></td><td></td></tr>
<tr><td>Composite cure rate</td><td>57/89 (64.0)</td><td>43/99 (43.4)</td></tr>
<tr><td>Difference between groups</td><td colspan="2">20.6% (95% CI 6.3% to 33.7%)</td></tr>
</table>

- Composite cure rate at test-of-cure visit in patients with levofloxacin-resistant, ESBL-producing pathogens at baseline

<table>
<tr><th></th><th>Ceftolozane/ tazobactam, n (%)</th><th>Levofloxacin, n (%)</th></tr>
<tr><td>Microbiological modified ITT population[c]</td><td>28/48 (58.3)</td><td>15/43 (34.9)</td></tr>
<tr><td>Difference between groups</td><td colspan="2">23.4% (95% CI 2.9% to 41.3%)</td></tr>
<tr><td>Per-protocol population[d]</td><td>28/43 (65.1)</td><td>15/36 (41.7)</td></tr>
<tr><td>Difference between groups</td><td colspan="2">23.4% (95% CI 1.5% to 42.6%)</td></tr>
</table>

</td><td>"In summary, 26.5% of cUTI patients from a large, international, multicentre randomized trial had baseline organisms that were resistant to levofloxacin, providing additional evidence of the waning clinical utility of fluoroquinolones as empirical agents against Gram-negative bacteria. Among these patients, ceftolozane/tazobactam demonstrated better composite cure, clinical cure and microbiological eradication rates compared with those of levofloxacin. Composite cure rates were lower for both treatment arms when compared with those of the general study population, suggesting that levofloxacin resistance is an independent predictor of treatment failure due to both therapeutic limitations and host factors and comorbidities. These clinical data indicate that high urine concentrations achieved with the highest approved dose of levofloxacin given for 7 days are not sufficient to overcome levofloxacin resistance in most instances. Ceftolozane/tazobactam offers an effective alternative empirical treatment for cUTI in settings of increasing fluoroquinolone resistance." Page 2019</td></tr>
</table>

AE = adverse event; CI = confidence interval; cIAI = complicated intra-abdominal infection; cLUTI = complicated lower-urinary-tract infection; ESBL = extended spectrum beta-lactamase; ITT = intention-to-treat; ME = microbiologically evaluable; *P. aeruginosa* = *Pseudomonas aeruginosa*; vs. = versus.

[a] ME population defined as all randomized patients who received protocol-specified amount of study drug, met the protocol-specific disease definition of cIAI, adhered to trial procedures, had a test-of-cure visit within 24–32 days of starting treatment, and had at least one baseline infecting pathogen identified that was susceptible to study drug.

[b] Microbiological ITT population defined as all randomized patients who had at least one pathogen identified in the abscess or peritoneal fluid at baseline, regardless of susceptibility to the study drug.

[c] Microbiological modified ITT population defined as all randomized patients who received at least one dose of study drug and had a positive urine culture (one or two uropathogens of at least 10^5 colony-forming units per mL) at baseline.

[d] Per-protocol population defined as patients in the modified microbiological ITT 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."[8]