The safety of ceftolozane-tazobactam for the treatment of acute bacterial infections: a systemic review and meta-analysis

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Abstract

Objective(s): The aim of this study was to conduct a meta-analysis to assess the clinical safety of ceftolozane-tazobactam for the treatment of acute bacterial infections in adult patients.

Methods: The PubMed, Embase, and Cochrane databases were searched from their inception until May 2020 for relevant randomized controlled trials (RCTs). Only RCTs evaluating the risk of adverse events (AEs) for ceftolozane-tazobactam and comparative treatments for acute bacterial infections in adult patients were included.

Results: Overall, four RCTs including a total of 2924 patients (1475 in the ceftolozane-tazobactam group and 1449 in the control group) were included in the meta-analysis. The rate of treatment-emergent AEs was 51.3% (748/1458) in the ceftolozane-tazobactam group, which was comparable to the control group, 49.9% [714/1430; odd's ratio (OR), 1.06; 95% confidence interval (CI), 0.91–1.25; $I^2 = 0\%$]. In addition, no difference was observed between the ceftolozane-tazobactam and control groups in terms of the risk of serious AEs (OR, 1.22; 95% CI, 0.93–1.61; $I^2 = 15.5\%$) and the risk of discontinuing the study drug due to AEs (OR, 0.85; 95% CI, 0.55–1.33; $I^2 = 0\%$). The rate of all-cause mortality did not significantly differ between the ceftolozane-tazobactam and control groups (OR, 1.11; 95% CI, 0.82–1.50; $I^2 = 0\%$). The only exception was the risk of *Clostridiodes difficile* (*C. difficile*) colitis, where ceftolozane-tazobactam treatment was associated with a significantly higher risk compared with the control group [0.72% (10/1376) *versus* 0.14% (2/1391), OR, 3.84; 95% CI, 1.23–11.97; $I^2 = 0\%$].

Conclusion: Ceftolozane-tazobactam treatment is as tolerable as comparative treatment options for acute bacterial infections in adult patients, however it has an increased risk of *C. difficile* infection. As a novel broad-spectrum antibiotic, ceftolozane-tazobactam could be a safe therapeutic option for use in common clinical practice.

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Plain language summary

The safety of ceftolozane-tazobactam (an antibiotics) for the treatment of acute bacterial infections

Objective(s): Ceftolozane-tazobactam is an effective antibiotic for the treatment of acute bacterial infections. This study conducts a meta-analysis to assess the clinical safety (side effects) of ceftolozane-tazobactam for the treatment of acute bacterial infections in adult patients compared with other drugs. **Methods:** We extracted data from four randomized controlled trials, including a total of 2924 patients (1475 in the ceftolozane-tazobactam group and 1449 in the control group). **Results:** The rate of treatment related adverse events (AEs) was similar in the ceftolozane-tazobactam group (51.3%) and control group (49.9%). There was also no difference in risk of serious adverse events, the risk of discontinuing the study drug due to AEs, and all-cause mortality. The only exception was the risk of *Clostridiodes*

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difficile colitis (a cause of antibiotic-associated diarrhea), where ceftolozane-tazobactam treatment was associated with a significantly higher risk compared with the control group. **Conclusion:** In conclusion, as a novel broad-spectrum antibiotic, ceftolozane-tazobactam could be a safe therapeutic option for use in clinical practice.

Introduction

Ceftolozane-tazobactam is a combination of the broad-spectrum cephalosporin and a ß-lactamase inhibitor.[1] Ceftolozane, an oxyimino-aminothiazolyl cephalosporin, is structurally similar to ceftazidime, but the *in vitro* increases in the minimum inhibitory concentration (MIC) of ceftazidime due to porin loss, are not observed for ceftolozane.[2] Tazobactam, a β-lactam sulfone, is a potent β-lactamase inhibitor of most common class A and C β-lactamases.[1] Many *in vitro* studies[3–7] have shown that this novel combination exhibits potent activity against most clinically important gram-negative bacteria, including multidrug-resistant (MDR) bacteria. Clinically, ceftolozane-tazobactam has also shown favorable efficacy for the treatment of complicated intra-abdominal infection (cIAI) and uncomplicated/complicated urinary tract infection (cUTI) in Japan.[8,9] In addition, several randomized controlled trials (RCTs) have demonstrated that the clinical efficacy of ceftolozane-tazobactam is comparable with other alternative agents for the treatment of acute bacterial infections.[10–12] In the ASPECT-cUTI trial,[10] ceftolozane-tazobactam was non-inferior to levofloxacin for composite cure (76.9% *versus* 68.4%, 95% CI 2.3–14.6) for the treatment of complicated lower-UTIs or pyelonephritis. In the ASPECT-cIAI trial,[11] the clinical response of ceftolozane-tazobactam plus metronidazole was comparable to meropenem in adult patients with cIAIs, including MDR pathogen-associated infections. In the ASPECT-NP trial,[12] high-dose ceftolozane-tazobactam was non-inferior to meropenem in terms of both the 28-day all-cause mortality and the clinical cure at test for Gram-negative nosocomial pneumonia in mechanically ventilated patients.[12] Even in the *post hoc* analysis of these RCTs,[13–15] the clinical efficacy of ceftolozane-tazobactam was non-inferior to comparative treatments for infections caused by antibiotic-resistant pathogens, including ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*, MDR *Pseudomonas aeruginosa*, and levofloxacin-resistant Enterobacteriaceae. In addition, empiric use of ceftolozane/tazobactam for the treatment of cUTI could also be a cost-effective choice.[16] These findings suggest that ceftolozane-tazobactam could be an effective antibiotic for the treatment of acute bacterial infections. In addition to clinical efficacy, safety issues are another important concern when physicians use novel antibiotics in clinical practice. However, an updated meta-analysis comparing the safety of ceftolozane-tazobactam with comparative drugs for the treatment of acute bacterial infection is lacking. We conducted this meta-analysis to provide evidence on the safety of ceftolozane-tazobactam in adult patients with acute bacterial infection.

Materials and methods

Study search and selection

This study was written and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[17] All clinical studies were identified through a systematic search of the PubMed, Embase, and Cochrane databases from their inception until May 2020. The following search terms were used: 'ceftolozane-tazobactam,' 'ceftolozane,' 'tazobactam,' and 'randomized'. Only RCTs that compared the risk of adverse events (AEs) for ceftolozane-tazobactam and comparative treatments for adult patients with acute bacterial infections were included. Articles published in all languages were eligible for inclusion. However, we excluded articles if they reported *in vitro* studies or pharmacokinetic–pharmacodynamic assessments. Two reviewers searched and examined the publications independently to avoid bias. Any disagreement was resolved and decided by a third reviewer. The following data was extracted from

the included studies: authorship, year of publication, study design, countries, antibiotic regimen for ceftolozane-tazobactam and the comparative treatment, and the risk of AEs.

Definitions and outcomes

The primary outcome was the risk of AEs, including treatment-emergent AEs (TEAE), treatment-related AEs, serious AEs, discontinuation of the study drug due to an AE, and all-cause mortality. TEAEs were defined as an AE that occurred in a participant that was administered the study drug but that does not necessarily have a causal association with the study drug. Serious AEs were defined as AEs that could result in death, persistent or significant disability or incapacity, be life threatening, require or prolong an existing hospitalization, or another important medical event deemed such by medical or scientific judgment.

Quality assessment

The quality of each included study was assessed using a risk-of-bias assessment tool.[18] Two reviewers subjectively reviewed all included studies and rated them either 'low risk', 'high risk', or 'unclear' according to the following items: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and inclusion of intention-to-treat analyses.

Data analysis

A DerSimonian–Laird random-effects model was performed to calculate the pooled estimates of odd's ratios (ORs).[19] A two-sided *p*-value of < 0.05 was considered to indicate a statistically significant difference. Study heterogeneity was presented using a χ^2-based Cochran's Q statistic and I^2. Cochran's Q was defined by summing the square of the amount that each study estimate deviated from the overall estimate. For the Q statistic, $p < 0.10$ were considered statistically significant for heterogeneity. For the I^2 statistic, heterogeneity was assessed as follows: no heterogeneity ($I^2 = 0$–25%), moderate heterogeneity ($I^2 = 25$–50%), large heterogeneity ($I^2 = 50$–75%), and extreme heterogeneity ($I^2 = 75$–100%). To evaluate the effect of individual studies, leave-one-out sensitivity analyses were performed for primary outcomes. In addition, publication bias

was assessed by using Doi plot and the asymmetry of Doi plot was examined by LFK index.[20] The Doi plot is more sensitive than the funnel plot if less than 10 studies are included. However, the publication bias could not be assessed if there are less than three studies included in the meta-analysis. All statistical analyses were performed using Review Manager (RevMan) version 5.3 and MetaXL.

Results

Study selection and characteristics

Our search yielded 150 results from Pubmed ($n = 23$), Embase ($n = 87$) and the Cochrane library ($n = 40$). After excluding 60 duplicates, we screened the titles and abstracts of the remaining 90 studies and seven were retrieved for a full-text review. Finally, four studies[10–12,21] fulfilled the inclusion criteria and were included in this meta-analysis (Figure 1). All studies[10–12,21] had a multicenter design (Table 1). Three RCTs[10–12] were phase III studies and one RCT[21] was a phase II study. Two studies focused on cIAI,[11,21] while one focused on cUTI[10] and one focused on nosocomial pneumonia.[12] The study by Kollef *et al.*[12] used high dose ceftolozane-tazobactam at 3 g every 8 h, while the other three RCTs[10,11,21] used 1.5 g ceftolozane-tazobactam every 8 h. Meropenem (three studies) and levofloxacin (one study) were used as the comparator treatments.

Overall, a total of 2924 patients (1475 in the ceftolozane-tazobactam group and 1449 in the control group) were included in this meta-analysis. Each study was classified as having a low risk of bias for all domains considered for analysis (Figure 2).

Risk of AEs

Overall, the rate of TEAEs was 51.3% (748/1458) in the ceftolozane-tazobactam group, which was comparable with the control group at 49.9% [714/1430; OR, 1.06; 95% confidence interval (CI), 0.91–1.25; $I^2 = 0$%; Figure 3]. In addition, no significant difference was observed between ceftolozane-tazobactam and the control group for the risk of serious AEs (OR, 1.21; 95% CI, 0.91–1.60; $I^2 = 16$%; Figure 3) and the risk of discontinuation of the study drug due to AEs (OR, 0.85; 95% CI, 0.55–1.33; $I^2 = 0$%; Figure 3). The rate of all-cause mortality did not differ significantly between the ceftolozane-tazobactam and the
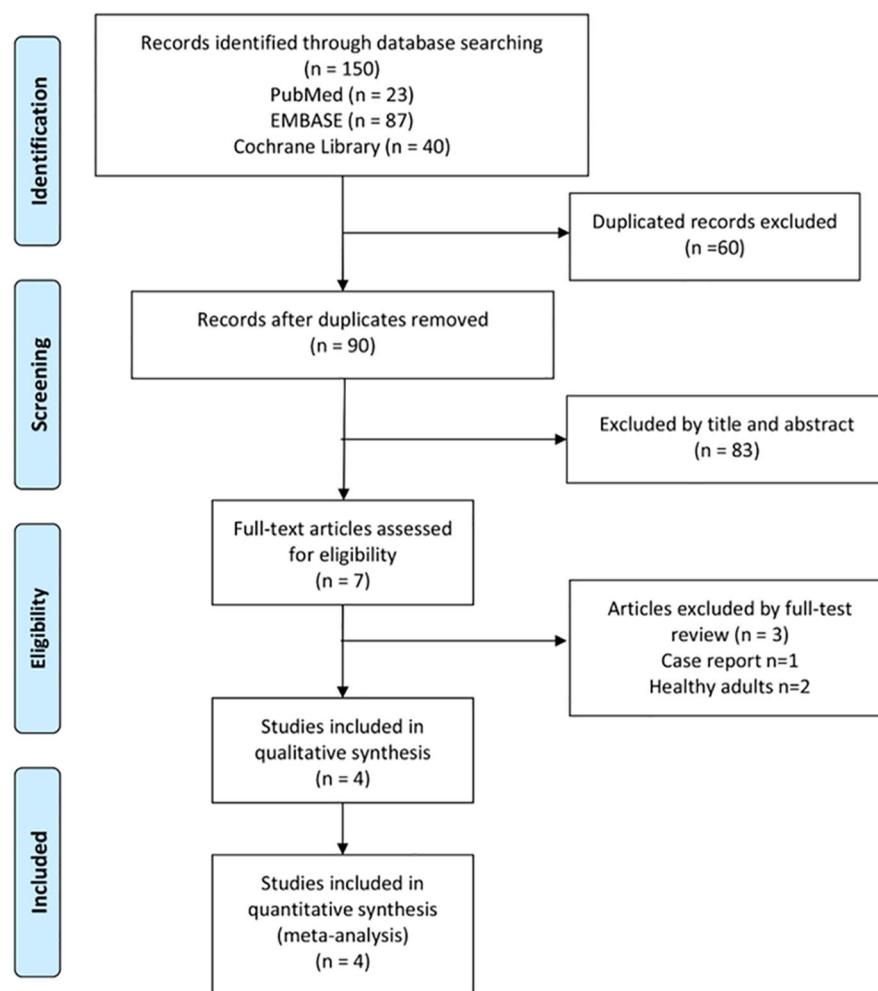
Figure 1. Algorithm for screening and identifying studies.

Table 1. Characteristics of included studies.

Study	Study design	Inclusion criteria	No. of patients	Dose regimen	
				Ceftolozane-tazobactam	Comparator
Lucasti et al.[21]	Multicenter, randomized double-blind, phase II trial	18–90 years old, had evidence of cIAI requiring surgical intervention, had one of the following diagnosis: cholecystitis with rupture or perforation, diverticular disease with perforation or abscess, appendiceal perforation or periappendiceal abscess, acute gastric or duodenal perforation, traumatic perforation of the intestine, peritonitis due to perforated viscus, IAI following a prior operative procedure, postoperative peritonitis, or intra-abdominal abscess	122	Ceftolozane-tazobactam 1.5 g plus metronidazole 500 mg every 8 h	Meropenem 1.0 g every 8 h
Solomkin et al.[11] (ASPECT-cIAI)	Multicenter, prospective, randomized, double blind, phase III trials	Aged 18 years or older, with clinical evidence of cIAI. Operative or percutaneous drainage of an infectious focus was either planned or had been performed recently (within 24 h), confirming the presence of cIAI.	993	Ceftolozane-tazobactam 1.5 g plus metronidazole 500 mg every 8 h	Meropenem 1.0 g every 8 h

Continued)

Table 1. (Continued)

Study	Study design	Inclusion criteria	No. of patients	Dose regimen	
				Ceftolozane-tazobactam	Comparator
Wagenlehner *et al.*[10] (ASPECT-cUTI)	Multicenter, randomized, double-blind, phase III trial	Aged 18 years or older, had pyuria, a diagnosis of pyelonephritis or cUTIs, 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	1083	Ceftolozane-tazobactam 1.5 g every 8 h	Levofloxacin 750 mg everyday
Kollef *et al.*[12] (ASPECT-NP)	Multicenter, randomized double-blind, phase III trial	Aged 18 years or older, were intubated and mechanically ventilated, and had VAP or ventilated HAP	726	Ceftolozane-tazobactam 3 g every 8 h	Meropenem 1.0 g every 8 h

cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

control groups (OR, 1.11; 95% CI, 0.82–1.50; $I^2 = 0$%; Figure 3). Only two RCTs reported the rate of treatment-related AEs, and the pooled analysis for these two RCTs showed that the risk of treatment-related AEs was similar between the ceftolozane-tazobactam and control groups (OR, 055; 95% CI, 0.07–4.05; $I^2 = 92$%; Figure 3).

In the subgroup analysis, which compared ceftolozane-tazobactam and meropenem, no significant difference was observed for the risk of TEAEs (OR, 1.10; 95% CI, 0.89–1.35; $I^2 = 0$%), serious AEs (OR, 1.29; 95% CI, 0.97–1.71; $I^2 = 10$%), discontinuation of the study drug due to TEAEs (OR, 0.85; 95% CI, 0.55–1.33; $I^2 = 0$%) or all-cause mortality (OR, 1.10; 95% CI, 0.81–1.49; $I^2 = 0$%.). In addition, the pooled analysis of the three phase III RCTs revealed that a similar trend was observed between ceftolozane-tazobactam and alternative antibiotics in terms of the risk of TEAEs (OR, 1.06; 95% CI, 0.90–1.25; $I^2 = 0$%), serious AEs (OR, 1.19; 95% CI, 0.94–1.51; $I^2 = 0$%), discontinuation of the study drug due to TEAEs (OR, 0.85; 95% CI, 0.55–1.33; $I^2 = 0$%), and all-cause mortality (OR, 1.09; 95% CI, 0.81–1.48; $I^2 = 0$%).

Regarding specific AEs, nausea was the most common AE (5.3%), followed by diarrhea (4.6%), headache (4.2%), anemia (4.0%), and pyrexia (3.9%). However, no significant difference was observed between ceftolozane-tazobactam and the control groups for the risk of elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase

Figure 2. Risk of bias summary.

(GGT), anemia, atrial fibrillation, diarrhea, dizziness, headache, hypokalemia, hypertension, ileus, insomnia, nausea, urinary tract infection, vomiting, or wound dehiscence (Table 2). The only
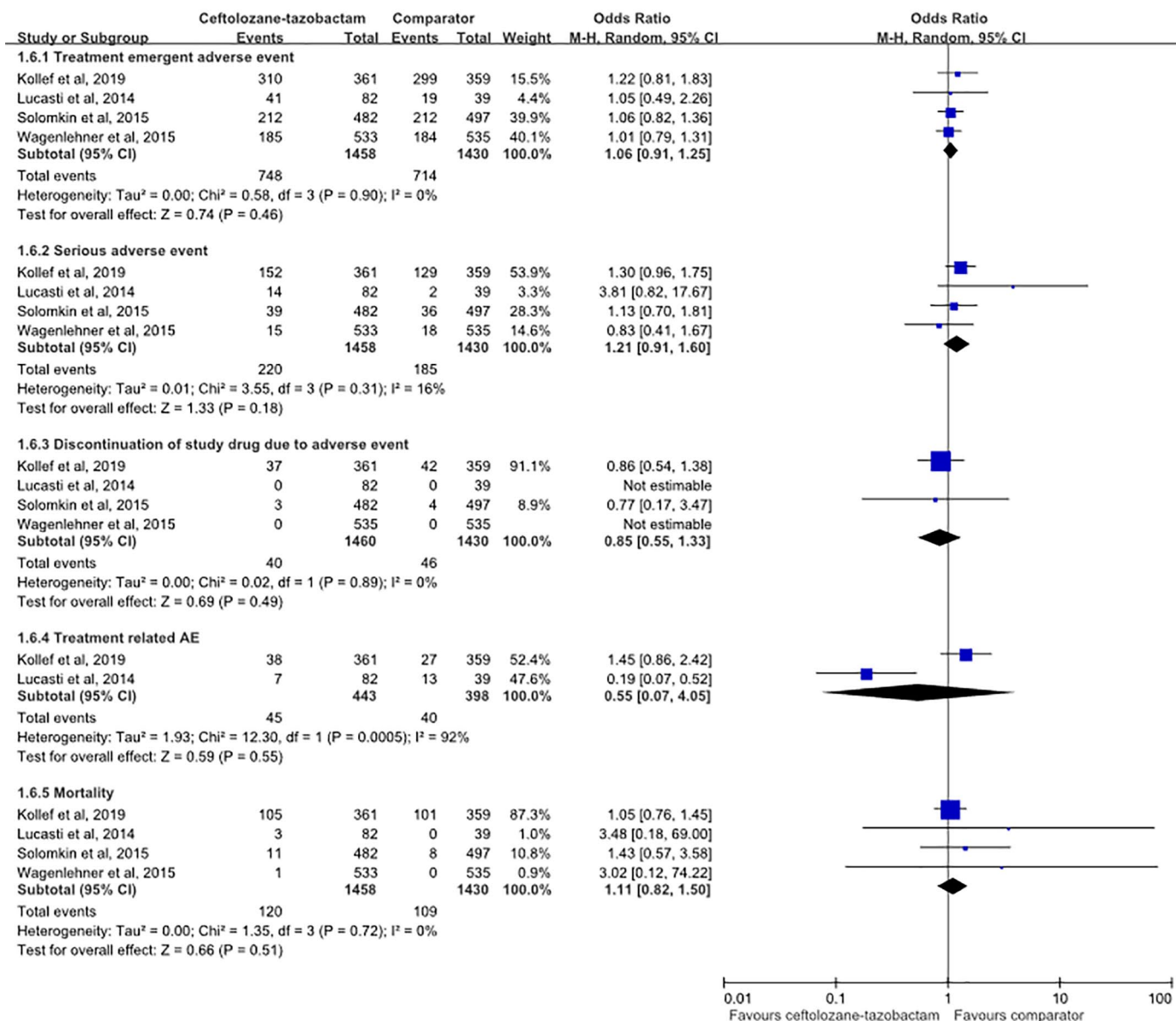
Figure 3. Forest plot of risks of adverse events (AEs).

exception was the risk of *Clostridiodes difficile* colitis, where ceftolozane-tazobactam was associated with a significantly higher risk compared with the control group [0.72% (10/1376) *versus* 0.14% (2/1391), OR, 3.84; 95% CI, 1.23–11.97; $I^2 = 0\%$] (Table 2).

Sensitivity analyses
Leave-one-out sensitivity analyses were performed to examine whether a single study may have any effect on the pooled results when

included studies were removed one at a time. The results showed that no study had significant influences on all primary outcomes, except for TRAEs, where only two studies were included with opposite direction of association (Table 3).

Publication bias
There was minor asymmetry for treatment-emergent AEs (LFK index = 1.34) and serious AEs (LFK index = 1.03), and major asymmetry for

Table 2. Risk of specific AEs.

AE	No of study	Rate of AE (%)		OR	95% CI	I^2, %
		Ceftolazone-tazobactam	Control group			
Gastrointestinal system						
Nausea	3	5.3	3.9	1.35	0.90–2.02	0
Diarrhea	4	4.6	5.3	0.81	0.50–1.32	45.6
Constipation	3	2.8	2.4	1.13	0.71–1.80	0
Vomiting	4	2.6	2.7	0.92	0.58–1.46	0
Upper abdominal pain	2	1.3	0.8	1.64	0.69–3.88	0
Ileus	2	0.7	0.2	2.36	0.38–14.75	0
Central nervous system						
Headache	2	4.2	3.4	1.25	0.80–1.97	0
Insomnia	2	2.4	2.4	0.92	0.30–2.84	74.1
Dizziness	2	1.0	0.6	1.79	0.36–8.88	61.7
Cardiovascular system						
Hypertension	4	2.3	2.0	1.00	0.46–2.15	51.9
Atrial fibrillation	3	1.7	2.1	1.02	0.35–2.00	39.9
Infection						
Urinary tract infection	3	2.5	2.4	1.00	0.61–1.63	0
Clostridioides difficile colitis	3	0.7	0.1	3.84	1.23–11.97	0
General						
Pyrexia	4	3.9	2.5	1.45	0.95–2.20	0
Local						
Phlebitis	2	0.7	1.3	0.43	0.13–1.47	0
Wound dehiscence	2	0.2	0.6	0.22	0.01–4.92	56.8
Laboratory						
Anemia	4	4.0	3.6	1.10	0.73–1.67	5.6
Hypokalemia	3	3.1	2.8	1.13	0.60–2.13	17.6
ALT increased	4	2.5	1.9	1.06	0.41–2.70	62.9
AST increased	4	2.3	1.7	1.23	0.54–2.82	45.2
GGT increased	2	0.7	1.3	0.47	0.14–1.58	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, γ-glutamyl transferase; OR, odd's ratio.

Table 3. Leave-one-out sensitivity analyses for AEs.

Study name	Statistics with study removed			
	OR	Lower limit	Upper limit	*p*-value
Treatment-emergent AE				
Lucasti *et al.*[21]	1.06	0.90	1.25	0.467
Wagenlehner *et al.*[10]	1.10	0.89	1.35	0.386
Solomkin *et al.*[11]	1.07	0.87	1.31	0.540
Kollef *et al.*[12]	1.04	0.87	1.23	0.694
Serious AE				
Lucasti *et al.*[21]	1.19	0.94	1.51	0.156
Wagenlehner *et al.*[10]	1.29	0.97	1.71	0.080
Solomkin *et al.*[11]	1.25	0.76	2.07	0.383
Kollef *et al.*[12]	1.15	0.67	1.98	0.604
Discontinuation of the study drug due to an AE				
Solomkin *et al.*[11]	0.86	0.54	1.38	0.534
Kollef *et al.*[12]	0.77	0.17	3.47	0.736
Treatment-related AE				
Lucasti *et al.*[21]	1.45	0.86	2.42	0.161
Kollef *et al.*[12]	0.19	0.07	0.52	0.001
Mortality				
Lucasti *et al.*[21]	1.09	0.81	1.48	0.562
Wagenlehner *et al.*[10]	1.10	0.81	1.49	0.549
Solomkin *et al.*[11]	1.07	0.78	1.48	0.664
Kollef *et al.*[12]	1.62	0.69	3.77	0.267

AE, adverse event; OR, odd's ratio

all-cause mortality (LFK index = 7.42) (Figure 4), which indicated moderate or substantial publication bias for primary outcomes. Publication bias was not assessed for the outcomes – the risk of discontinuation of the study drug due to an adverse event and TRAEs because only two studies were included.

Discussion

This meta-analysis of four RCTs[10–12,21] demonstrated that the safety of ceftolozane-tazobactam is comparable to that of alternative treatment options for patients with acute bacterial infections; this is supported by the following evidence. Firstly, in the pooled analysis of four RCTs,[10–12,21] the overall risk of TEAEs, serious AEs, discontinuation of the study drug due to TEAEs, treatment-related AEs, and all-cause mortality for ceftolozane-tazobactam were similar to that of the comparison drug. This finding was consistent with previous meta-analysis with only three RCTs investigating the clinical efficacy and safety of ceftolozane-tazobactam.[22,23] Secondly, no significant differences were observed in the subgroup analysis of only phase III trials[10–12] that compared ceftolozane-tazobactam with alternative antibiotics and only RCTs[11,12,21] that compared ceftolozane-tazobactam with meropenem. Thirdly, the risks for almost all specific AEs, except for the risk of *C. difficile* colitis, were similar between ceftolozane-tazobactam and the alternative treatment options. Finally, the overall risk of TEAEs, serious AEs, and discontinuation of the study drug due to TEAEs were 15.7%, 2.7%, and 8.2%, respectively. Although the overall all-cause mortality rate was 8.2% (*n* = 120) for ceftolozane-tazobactam, most of the deaths were from the study by Kollef *et al.*,[12] which included patients with nosocomial pneumonia, in which the mortality rate was 29.1% (*n* = 105).[12] In contrast, only 15 deaths were reported in the three other studies[10,11,21] for patients with cIAI and cUTI, and the pooled mortality was only 1.4%. These findings are consistent with those of previous retrospective studies,[8,9] in which ceftolozane-tazobactam treatment was well tolerated for the treatment of acute bacterial infection. A multicenter, open-label, non-comparative study[8] investigated the usefulness of ceftolozane-tazobactam plus metronidazole in 100 Japanese patients with cIAI. It revealed that the rate of TEAEs, serious AEs, and drug-related AEs were 62%, 10%, and 19%, respectively; however, no drug related serious AEs were observed and no patients discontinued the drug due to an AE. Another nonrandomized, multi-center, open-label study[9] assessed the usefulness of ceftolozane-tazobactam in 114 Japanese patients with cUTI. It reported that the rate of TEAEs and drug-related AEs were 57.8% and 17.5%, respectively. AEs leading to ceftolozane-tazobactam discontinuation were observed in two patients, one patient with a moderate headache and the other with mild hepatic function abnormality, but no drug related serious AEs or death were reported. In summary, these findings
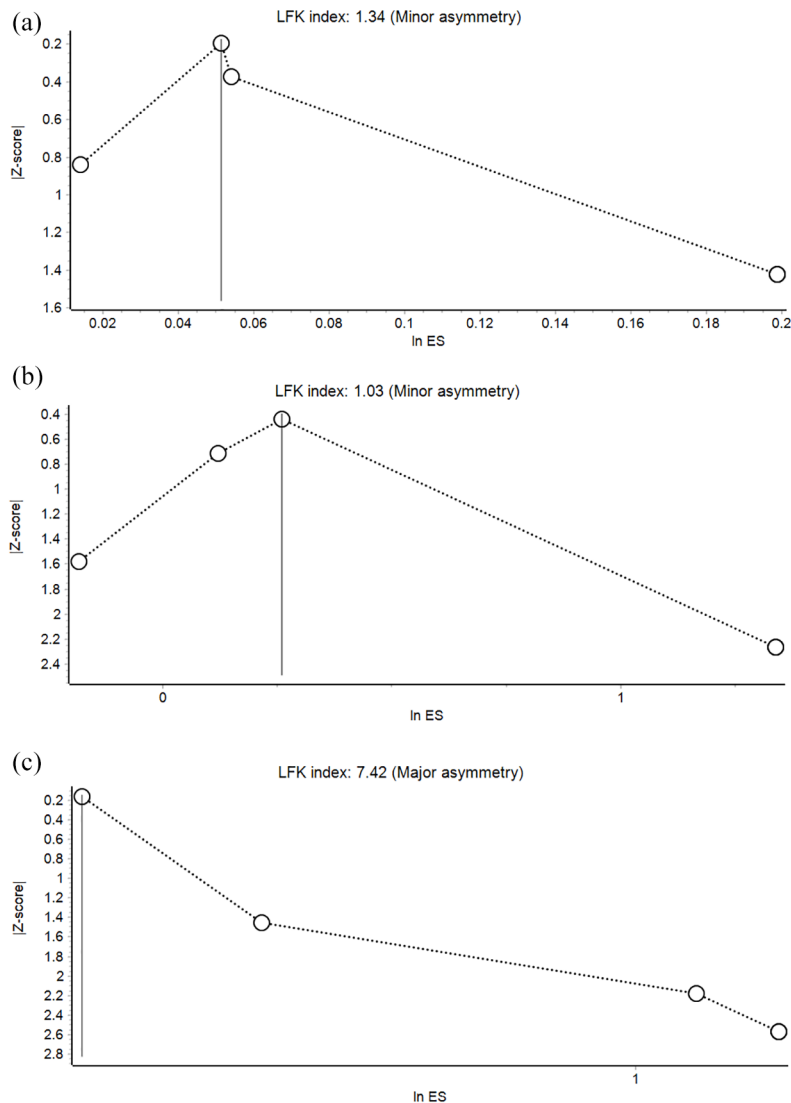
Figure 4. Publication of bias according to the outcome of (a) treatment-emergent adverse events (AEs), (b) serious AE, and (c) major asymmetry for all-cause mortality.

suggest that ceftolozane-tazobactam is a tolerable therapeutic option for the treatment of acute bacterial infections.

In contrast to previous meta-anlaysis,[22,23] the present meta-analysis did a comprehensive investigation about the risk of each specific AE. In this meta-analysis, the gastrointestinal system was the most common system affected by AEs. The most common AE was nausea (5.3%) while the frequencies of all other AEs were <5%. Most importantly, most AEs in the included studies were mild to moderate.[10–12,21] In the study by Solomkin *et al.*,[11] the most common laboratory AEs were

increased ALT and AST, which occurred in 2.5% and 1.6% of all patients, respectively. In the study by Wagenlehner *et al.*[10] the most common AEs were mild to moderate, and the incidence of treatment-limiting adverse events was <2% in each treatment group, while no laboratory abnormality resulted in an AE that led to premature discontinuation of the study drug. In the study by Kollef *et al.*,[12] the most commonly reported treatment-related AEs in the ceftolozane–tazobactam group were abnormal liver function tests (3.3%, $n = 12$), *C. difficile* colitis (1.1%, $n = 4$), and diarrhea (1.1%, $n = 4$). In the single arm study by Arakawa *et al.*,[9] the most common drug-related

AEs were diarrhea and ALT increase (5.3% each), while AST increased in 3.5% of patients. In another single arm study by Mikamo et al.,[8] the most common drug-related AEs were AST increase (11.0%), ALT increase (9.0%), diarrhea (3.0%), and nausea (2.0%). All cases of ALT or AST increase were resolved by the end of the treatment or during the study. Based on the findings of observational studies, Maraolo et al.[24] conducted a systematic review of the efficacy and safety of off-label use of ceftolozane-tazobactam in the treatment of a total of 130 difficult-to-treat *Pseudomonas aeruginosa* infections and found that only five AEs occurred among 48 available cases, including hypokalemia ($n = 2$), and each one of *C. difficile* infection, rash, and elevation of liver enzyme. In summary, gastrointestinal AEs and abnormal liver function were the most common AEs associated with ceftolozane-tazobactam, but most of them were mild to moderate.

In this meta-analysis, we found that *C. difficile* infection could be a concern when ceftolozane-tazobactam is administered. In the study by Solomkin et al.,[11] ceftolozane-tazobactam-related serious AEs due to *C. difficile* infection were reported in one patient (0.21%). In the study by Kollef et al.,[12] ceftolozane-tazobactam related *C. difficile* colitis was reported in four patients (1.1%), while in Wagenlehner et al.'s study[10] two serious AEs (0.38%) due to *C. difficile* infection were reported in the ceftolozane-tazobactam group, and these were deemed to be associated with the study treatment. These two patients had recovered by the follow-up. In Maraolo et al.'s[24] systematic review, the risk of *C. difficile* infection was 2.1% (2/48).[24] Although none of the *C. difficile* infections were reported to cause death, the pooled analysis of these three RCTs showed that the overall risk of *C. difficile* colitis was 0.7%, which was significantly higher than in the comparative treatments. As a result, clinicians should keep alert to the risk of *C. difficile* colitis when treating patients with ceftolozane-tazobactam.

A limitation of the current study was that only four RCTs were considered within the meta-analysis, and only three types of acute bacterial infections (pneumonia, cUTI, and cIAI) were included. In addition, four RCTs included different patients' population and control groups are not all the same. Further large-scale research is warranted to assess the usefulness of ceftolozane-tazobactam as a treatment.

In conclusion, the safety profile of ceftolozane-tazobactam does not significantly differ from that of comparator drugs for the treatment of acute bacterial infections in adult patients. However, it has an increased risk of *C. difficile* infections. As a novel broad-spectrum antibiotic, ceftolozane-tazobactam could be a safe therapeutic option for use in common clinical practice.

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