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MAJOR ARTICLE

Novel Beta-Lactam/Beta-Lactamase Plus Metronidazole vs Carbapenem for Complicated Intra-abdominal Infections: A Meta-analysis of Randomized Controlled Trials

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Background. Complicated intra-abdominal infections (cIAIs) remain a leading cause of death in surgical wards, in which antibiotic treatment is crucial. We aimed to compare the efficacy and safety of novel β-lactam/β-lactamase inhibitors (BL/BLIs) in combination with metronidazole and carbapenems in the treatment of cIAIs.

Methods. A comprehensive search of randomized controlled trials (RCTs) was performed using Medline, Embase, and Cochrane Library, which compared the efficacy and safety of novel BL/BLIs and carbapenems for the treatment of cIAIs.

Results. Six RCTs consisting of 2254 patients were included. The meta-analysis showed that novel BL/BLIs in combination with metronidazole had a lower clinical success rate (risk difference [RD], −0.05; 95% CI, −0.07 to −0.02; I^2 = 0%) and a lower microbiological success rate (RD, −0.04; 95% CI, −0.08 to −0.00; I^2 = 0%). No difference was found between the 2 groups in incidence of adverse events (RD, 0.02; 95% CI, −0.01 to 0.06; I^2 = 0%), serious adverse events (SAEs; RD, 0.01; 95% CI, −0.02 to 0.03; I^2 = 0%), or mortality (RD, 0.01; 95% CI, −0.00 to 0.02). However, ceftazidime/avibactam had a higher risk of vomiting (RD, 0.03; 95% CI, 0.01 to 0.05; I^2 = 47%), and the ceftolozane/tazobactam subgroup showed a higher incidence of SAEs (RD, 0.12; 95% CI, 0.01 to 0.03).

Conclusions. The efficacy of novel BL/BLIs in combination with metronidazole was not as high as that of carbapenems. Although no significant differences were found with respect to overall adverse events, SAEs, or mortality, the novel BL/BLIs has a higher risk of vomiting. We still need to be cautious about the clinical application of a new anti-infective combination.

Trial registration. PROSPERO ID: 42020166061.

Keywords. β-lactam/β-lactamase inhibitors; carbapenems; complicated intra-abdominal infections; meta-analysis.

Complicated intra-abdominal infections (cIAIs) remain the most common surgical infections, and this is the second most common site of invasive infections in critically ill patients [1], with an estimated overall mortality ranging from 10% to 35% [2]. They require both source control and anti-infective therapy [3, 4]. Enterobacteriaceae, *Streptococcus* species, and anaerobes are the most common microorganisms observed in community-acquired cIAIs (CA-cIAIs) [5], whereas other difficult-to-treat microorganisms, such as *P. aeruginosa,* can play a crucial role in health care–acquired cIAIs (HA-cIAIs) [6]. Empiric antibiotic therapy is important, especially in critically ill patients [7].

In principle, high-risk cIAI patients require broad-spectrum antibiotics covering resistant organisms, including gram-negative organisms, and anaerobes tailored to the institution-specific antibiogram [8]. Carbapenems have been increasingly used as a treatment option. However, the highly adaptive gram-negative pathogens can produce various β-lactamase enzymes that render them resistant to the antibiotic's mechanism of action [9], promoting medical practitioners to continuously explore and validate new alternative antibiotics for empiric therapy. Among the newer BL/BLIs recently approved for the management of cIAIs, imipenem/cilastatin/relebactam is approved for the treatment of cIAIs in monotherapy [10]. Only ceftolozone/tazobactam and ceftazidime/avibactam have been approved for treatment of cIAIs in combination with metronidazole. Thus, we conducted a meta-analysis of randomized controlled trials (RCTs) to clarify whether the use of BL/BLIs in combination with metronidazole was associated with improved outcomes compared with carbapenem for the treatment of cIAIs.

METHODS

Data Sources

Studies were identified by a systematic review of the literature in the PubMed, Embase, and Cochrane databases through February 2020 using the following search terms:

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"ceftazidime" OR "avibactam" OR "ceftazidime/avibactam" OR "ceftolozane" OR "tazobactam" OR "ceftolozane/tazobactam" AND "complicated intra-abdominal infection" OR "cIAIs" AND "randomized controlled trials" OR "randomized." To identify relevant unpublished studies, we searched ClinicalTrials.gov with the same search terms. In addition, references of all relevant articles that commented on novel BL/BLIs were also searched for eligible trials. Articles of all languages were included.

Selection Criteria

RCTs were considered eligible for inclusion if they directly compared the clinical efficacy and safety of novel BL/BLIs plus metronidazole with carbapenems in the treatment of cIAIs.

Studies were excluded if they focused on in vitro activity, were animal studies, or focused on pharmacokinetic/pharmacodynamic assessment. Moreover, studies that compared BL/BLI monotherapy with carbapenems were also excluded.

Qualitative Assessment

The Cochrane Collaboration Risk of Bias tool used to assess the methodological quality of included RCTs consisted of 7 modules as follows: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. The risk of bias was assessed by separately classifying each item as low, unclear, or high risk [11].

Data Extraction

Data search and extraction were performed by 2 investigators independently to ensure the reliability of data. Any controversial issue was resolved through discussion or seeking advice from supervisors. All data were recorded in a predesigned table. The following data were extracted and recorded: name and publication date; study design; interventions and population (microbiologically modified intention-to-treat [mMITT] population, clinically evaluable [CE] population, microbiologically evaluable [ME] population, and safety population); and baseline characteristics of patients.

Analyzed Outcomes

Efficacy outcomes included clinical cure rates, defined as resolution or improvement in signs and symptoms of the index infection, as well as microbiological cure rates or per-pathogen microbiological cure rates, defined as eradication of the baseline pathogen (if no postbaseline specimen was available for culture, microbiological outcome was based on clinical assessment). Safety outcomes included adverse events (AEs) and serious adverse events (SAEs), defined as events that resulted in death, were life-threatening, required hospitalization or prolonged hospitalization, or resulted in persistent or significant disability or incapacity.

Data Analysis and Statistical Methods

Statistical analysis was carried out using Review Manager 5.3. The degree of heterogeneity was evaluated with Q statistics generated from the χ^2 test, and I^2 was used to assess the proportion of statistical heterogeneity. Heterogeneity was defined as significant when $P < .10$ or $I^2 > 50\%$. The fixed-effects model was used when the data were homogenous, and the random-effects model was used when the data were heterogeneous. The pooled risk difference (RD) and 95% confidence interval were calculated for outcome analysis.

RESULTS

Study Selection and Characteristics

The search program yielded 71 references. After 18 nonclinical trials were excluded, the remaining 53 abstracts were screened. Among them, we retrieved 9 articles for full-text review. Finally, 6 studies fulfilling the inclusion criteria were included in this meta-analysis. Figure 1 illustrates the flow diagram consisting of the detailed screening and selection process for the trials included in our analysis.

Table 1 summarizes the basic characteristics of included trials. Six RCTs [12–17] included patients with cIAIs, and novel BL/BLIs were compared with meropenem in all patients, among which 4 studies focused on ceftazidime/avibactam plus metronidazole and 2 studies focused on ceftolozane/tazobactam. The subjects included in almost all articles [13–17] were hospitalized adults, except for 1 article [12], which included infants and children (≥3 months to <18 years) who required hospitalization and intravenous (IV) antibacterial therapy for cIAIs. There were 2 phase II studies [12, 16, 17] and 3 phase III studies [13–15]. Among the 4 studies focusing on ceftazidime/avibactam, 2000 mg of ceftazidime and 500 mg of avibactam were given via IV infusion, followed by IV infusion of 500 mg metronidazole every 8 hours for adults, while the dosage for children was adjusted according to weight and age. As for the other 2 studies focusing on ceftolozane/tazobactam, 1500 mg of ceftolozane/tazobactam (1000 mg of ceftolozane and 500 mg of tazobactam) and metronidazole (500 mg every 8 hours) were used. Dose adjustment of the study drug was necessary in all studies on the basis of creatinine clearance.

The Cochrane Risk of Bias assessment tool was used to assess the quality of our study. Figure 2 summarizes the risk of bias. Except for 1 article, the other 5 articles all had very low risk for sequence generation. Two articles did not make it clear whether the allocation concealment was conducted, 1 article, in which the random code assignment was performed by the unblinded pharmacist/designee, did not conduct allocation concealment, and the other 3 articles had very low risk for allocation

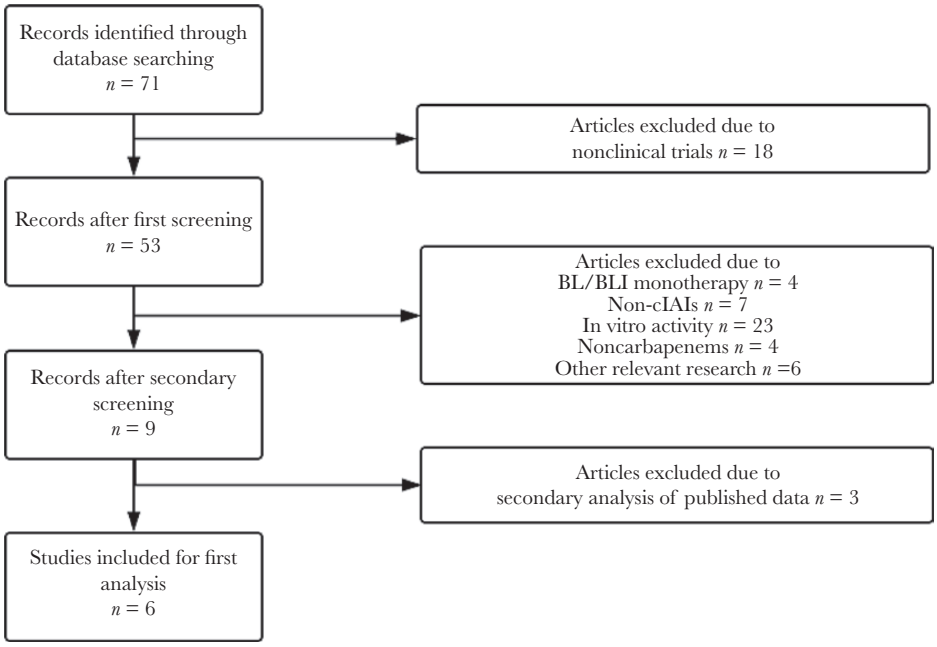

Figure 1. Flow diagram and references of included studies.

concealment. There was only 1 article with a single-blinded design, which had a high risk for performance bias, while the others only had low risk. All studies had low risk for detection and attrition bias and high risk for reporting bias.

Clinical Response

Six studies consisting of 2254 subjects all reported clinical success in the mMITT population. Overall, the treatment regimen of BL/BLIs in combination with metronidazole had a lower clinical success rate compared with meropenem (RD, –0.05; 95% CI, –0.07 to –0.02; I^2 = 0%) (Figure 3A). Subgroup analysis also showed the same trend: 4 RCTs including 1362 patients in the ceftazidime/avibactam subgroup (RD, –0.04; 95% CI, –0.08 to –0.00; I^2 = 0%) (Figure 3A) and 2 RCTs consisting of 892 patients in the ceftolozane/tazobactam subgroup (RD, –0.05; 95% CI, –0.10 to –0.00; I^2 = 35%) (Figure 3A).

Microbiological Response

In most patients, microbiological outcomes were presumed based on clinical outcomes, because intra-abdominal cultures require an invasive procedure and were therefore only obtained if clinically indicated.

Overall Microbiological Response

Four studies consisting of 1127 patients reported the overall incidence of favorable microbiological response, and pooled analysis showed that BL/BLIs combined with metronidazole had a lower overall microbiological response rate (RD, –0.04; 95% CI, –0.08 to –0.00; I^2 = 0%) (Figure 3B). This inferiority mainly came from the ceftazidime/avibactam subgroup (RD, –0.04; 95% CI, –0.08 to –0.00; I^2 = 0%) (Figure 3B), including 4 articles consisting of 1050 patients. One study consisting of 77 patients in the ceftolozane/tazobactam subgroup showed no difference between BL/BLIs and meropenem (RD, –0.05; 95% CI, –0.16 to 0.06) (Figure 3B).

Pathogen-Based Response

E. coli was the most common pathogen isolated from blood or the site of cIAIs; other common pathogens included *Klebsiella pneumoniae*, *Psudomonas aeruginosa*, anaerobe, *Bacteroides fragilis*, and *Enterococcus faecium*.

The microbiological response rate of *E. coli* was reported in 6 studies consisting of 1356 patients. In general, there was no significant difference between the control group and the experimental group (RD, –0.03; 95% CI, –0.06 to 0.00; I^2 = 2%) (Figure 3C). Moreover, ceftolozane/tazobactam subgroup analysis showed the same trend (2 RCTs, 496 patients; RD, 0.01; 95% CI, –0.04 to 0.05; I^2 = 0%) (Figure 3C). However, ceftazidime/avibactam subgroup analysis showed that ceftazidime/avibactam in combination with metronidazole had a relatively poor microbiological response to *E. coli* (4 RCTs, 860 patients; RD, –0.05; 95% CI, –0.10 to –0.01; I^2 = 0%) (Figure 3C).

For *Klebsiella pneumoniae*, the antibacterial ability of the ceftolozane/tazobactam subgroup was relatively insufficient (Supplementary Figure 1), while neither the overall results nor the results of the ceftazidime/avibactam subgroup showed any difference in microbiological response rates between the 2 groups (Supplementary Figure 1). Similarly, the results of other strains, including *Psudomonas aeruginosa*, anaerobe, *Bacteroides fragilis*, and *Enterococcus faecium*, showed that

Table 1. Basic Characteristics of Included RCTs

Author Year	Study Design	Sample		Gender		Age		Organism		BI/BIis Regime
		β	c	β	c	β	c	β	c	
Bradley, J. S. 2019	Phase 2, single-blind, randomized, multicenter, active-controlled study (NCT02475733)	mMITT (n = 50) CE (n = 56) ME (n = 40) Safety population (n = 61)	mMITT (n = 19) CE (n = 20) ME (n = 15) Safety population (n = 22)	Male 44	Male 9	Age, mean (range) 10.4 (3–17)	Age, mean (range) 10.1 (5–16)	Enterobacteriaceae 42 (84.0) *E. coli* 42 (84.0) *K. pneumoniae* 2 G^- pathogens other than Enterobacteriaceae 16 *Pseudomonas aeruginosa* 14 pathogens 26 *Streptococcus anginosus* group 23 *Enterococcus avium* 4 *Enterococcus faecium* 2 *Anaerobes* 24 *Enterococcus faecium* 14 *Enterococcus faecium* group 2 *Enterococcus avium*3 *Bacteroides ovatus* 2 *Bacteroides thetaiotaomicron* 3 *Bacteroides vulgatus* 2 *Clostridium perfringens* 0 *Clostridium ramosum* 2 *Eggerthella lenta* 2 *Parabacteroides distasonis* 2 *Parvimonas micra* 4 *Prevotella buccae* 2	Enterobacteriaceae 14 *E. coli* 13 *K. pneumoniae* 1 G^- pathogens other than Enterobacteriaceae 10 *Pseudomonas aeruginosa* 9 G^+ pathogens 11 *Streptococcus anginosus* group 10 *Enterococcus avium* 1 *Enterococcus faecium Anaerobes* 12 *Enterococcus faecium* 7 *Enterococcus faecium* group 2 *Enterococcus avium* 0 *Bacteroides ovatus* 0 *Bacteroides thetaiotaomicron* 3 *Bacteroides vulgatus* 0 *Clostridium perfringens* 2 *Clostridium ramosum* 0 *Eggerthella lenta* 0 *Parabacteroides distasonis* 0 *Parvimonas micra* 5 *Prevotella buccae* 0	CFT/TAZ i.v. over 2 h then MNZ i.v. over 20–30 min
Qin, X. 2017	RECLAIM 3 was a phase 3, multicenter, randomized, double-blind, double-dummy comparative study (NCT01726023)	mMITT (n = 143) CE (n = 177) ME (n = 99)	mMITT (n = 152) CE (n = 184) ME (n = 113)	Male 141	Male 153	Age, mean (SD) 48.5 (16.8)	Age, mean (SD) 48.5 (17.4)	The mMITT population comprised 295 subjects, of whom 239 (81.0%) had 1 or more Enterobacteriaceae isolates identified from the blood and/or intra-abdominal site. The most frequently reported Enterobacteriaceae were *E. coli* (173 subjects; 58.6%) and *K. pneumoniae* (63 subjects; 21.4%). Of the 47 subjects (15.9%) with non-Enterobacteriaceae G^- pathogens, *P. aeruginosa* was the most frequently reported (37 subjects; 12.5%)		CAZ/AVI 2000/500 mg as a 2-h i.v. followed by MNZ 500 mg as a 60-min i.v. every 8 h
Mazuski, J. E. 2016	Data from 2 identical, prospective, randomized, multicenter, double-dummy, double-blind, comparative global studies (NCT01499290 [RECLAIM 1] and NCT01500239 [RECLAIM 2]) were combined into a single inferential database with prespecified agreement from the US FDA and the European Medicines Agency	mMITT (n = 413) CE (n = 410) Safety population (n = 529)	mMITT (n = 410) CE (n = 416) Safety population (n = 529)	Male 326	Male 332	Age, mean (SD) 49.8 (17.5)	Age, mean (SD) 50.3 (18.3)	Enterobacteriaceae 323 *E.coli* 260 *K. pneumoniae* 47 Non-Enterobacteriaceae 39 *Pseudomonas aeruginosa* 32	Enterobacteriaceae342 *E. coli* 276 *K. pneumoniae* 48 Non-Enterobacteriaceae 47 *Pseudomonas aeruginosa* 36	CAZ/AVI (2000 mg of CAZ and 500 mg of AVI as a 2-hour i.v. every 8 h), followed by MNZ (500 mg as a 60-min i.v. every 8 h)

Table 1. Continued

Author Year	Study Design	Sample β	Sample c	Gender β	Gender c	Age β	Age c	Organism β	Organism c	BI/BIis Regime
Lucasti, C. 2013	Phase II, prospective, randomized, double-blind, active-controlled trial (ClinicalTrials.gov identifier: NCT00752219)	mMITT (n = 85) CE (n = 87) ME (n = 68)	mMITT (n = 89) CE (n = 90) ME (n = 76)	Male 70	Male 81	Age, mean + SD 43.0 + 15.9 (18–79)	Age, mean + SD 42.6 + 18.1 (18–88)	G^- aerobic pathogens (153 pathogens with susceptibility testing isolated from 127 patients) 147 6 *E. coli* (105 isolates) 105 (100%) 0 *K. pneumoniae* (17 isolates) 14 (82.4%) 3 (17.6) *Pseudomonas aeruginosa* (10 isolates) 8 (80%) 2 (20%) *Enterobacter cloacae* (5 isolates) 5 (100%) 0 *Klebsiella oxytoca* (4 isolates) 4 (100%) 0 *Acinetobacter baumannii* (2 isolates) 1 (50%) 1 (50%) *Proteus mirabilis* (2 isolates) 2 (100%) 0 *Pseudomonas fluorescens* (2 isolates) 2 (100%) 0other (6 isolates) 6 (100%) 0 G^+ pathogens (22 pathogens with susceptibility testing isolated from 19 patients) 13 9 *Staphylococcus aureus* (11 isolates) 5 (45.5%) 6 (54.5%) *Streptococcus agalactiae* (2 isolates) 2 (100%) 0 *Streptococcus constellatus* (1 isolate) 0 1 (100%) *Streptococcus intermedius* (2 isolates) 1 (50) 1 (50) *Streptococcus salivarius* (1 isolate) 0 1 (100) other (5 isolates) 5 (100) 0	G^- aerobic pathogens (153 pathogens with susceptibility testing isolated from 127 patients) 147 6 *E. coli* (105 isolates) 105 (100%) 0 0 *K. pneumoniae* (17 isolates) 17 (100%) 0 0 *Pseudomonas aeruginosa* (10 isolates) 9 (90%) 0 1 (10%) *Enterobacter cloacae* (5 isolates) 5 (100%) 0 0 *Klebsiella oxytoca* (4 isolates) 4 (100%) 0 0 *Acinetobacter baumannii* (2 isolates) 1 (50%) 0 1(50%) *Proteus mirabilis* (2 isolates) 2 (100%) 0 0 *Pseudomonas fluorescens* (2 isolates) 2 (100%) 0 0 other (6 isolates) 6 (100%) 0 0 G^+ pathogens (22 pathogens with susceptibility testing isolated from 19 patients) 19 0 3 *Staphylococcus aureus* (11 isolates) 8 (72.7%) 0 3 (27.3%) *Streptococcus agalactiae* (2 isolates) 2 (100%) 0 0 *Streptococcus constellatus* (1 isolate) 1 (100%) 0 0 *Streptococcus intermedius* (2 isolates) 2 (100%) 0 0 *Streptococcus salivarius* (1 isolate) 1 (100%) 0 0 other (5 isolates) 5 (100%) 0 0	2000 mg of CAZ + 500 mg of AVI given as an i.v. over 30 min every 8 h
Solomkin, J. 2015	Two identical multicenter, prospective, randomized, double-blind, placebo-controlled trials were initiated in December 2011 at 196 study centers worldwide (ClinicalTrials.gov identifiers NCT01445665 and NCT01445678)	mMITT (n = 389) ME (n = 275) CE (n = 375) Safety population (n = 482)	mMITT (n = 417) ME (n = 321) CE (n = 399) Safety population (n = 497)	Male 218	Male 248	Mean (SD) 50.8 (18.3)	Mean (SD) 50.4 (16.9)	"The incidence and distribution of baseline pathogens were similar between the treatment groups. The most common G^- aerobes isolated at baseline from intra-abdominal specimens in the MITT population were *E. coli* (525/806 [65.1%]), *K. pneumoniae* (76/806 [9.4%]), and *P. aeruginosa* (72/ 806 [8.9%]). The majority of infections were *polymicrobial* (257/389 [66.1%] and 288/417 [69.1%] patients in the CFT/TAZ + MNZ and meropenem treatment groups, respectively). There were 29 ESBL-producing Enterobacteriaceae isolated in each treatment group, an overall rate of 7.2% (58/806). Of 52 individual *P. aeruginosa* isolates for which MIC data were available, 3 (5.8%) isolates were resistant to ≥3 drug classes known to be active against *P. aeruginosa*, and 6 (11.5%) were nonsusceptible to ≥3 antipseudomonal drug classes."		CFT/TAZ 1.5 g (containing 1 g CFT and 500 mg TAZ) + MNZ (500 mg every 8 h)
Lucasti, C. 2014	Prospective, double-blind, randomized, multicenter phase II trial (ClinicalTrials.gov registration No. NCT01147640)	mMITT (n = 61) CE (n = 70) ME (n = 53)	mMITT (n = 25) CE (n = 35) ME (n = 24)	Sex, male 45 (54.9%)	Sex, male 24 (61.5%)	Age, (≥65) 19	Age, (≥65) 7	The incidence and distribution of intra-abdominal pathogens isolated at baseline were similar in the treatment groups. For the mMITT population, the most common pathogen isolated at baseline was *E. coli*, present in 41/61 (67.2%) and 19/25 (76.0%) patients in the CFT/TAZ and meropenem groups, respectively. In the mMITT population, 24/61 (39.3%) patients in the CFT/TAZ group and 9/25 (36.0%) patients in the meropenem group had a *polymicrobial* infection (≥2 organisms isolated at baseline).		i.v. CFT/TAZ (1.5 g every 8 h [q8h]) + i.v. MNZ (500 mg q8h)

Abbreviations: CAZ/AVI, ceftazidime/avibactam; CE, clinical evaluable; CFT/TAZ, ceftolozone/tazobactam; i.v., intravenous injection; ME, microbiological evaluable; mMITT, micro-modified intent-to-treat; MNZ, metronidazole.

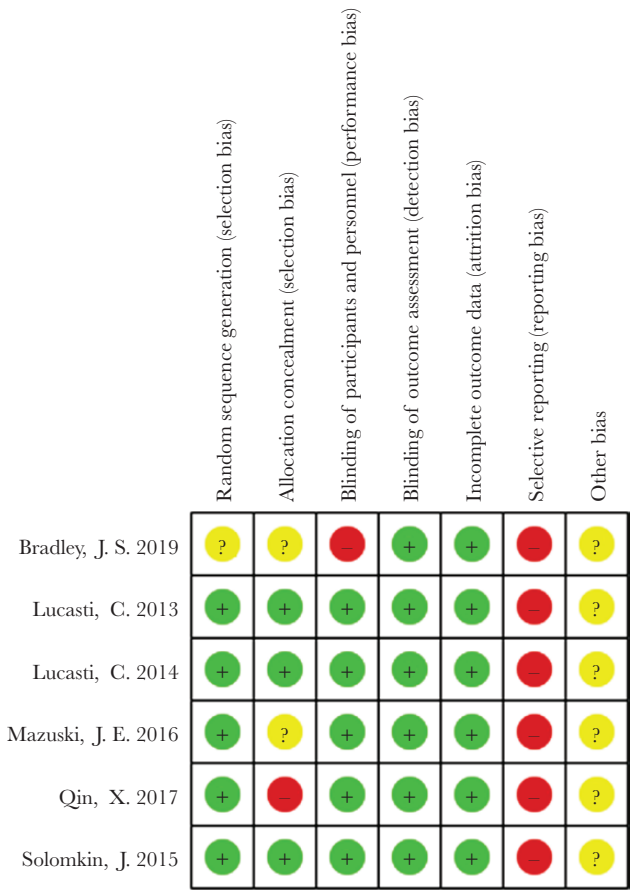

Figure 2. Risk of bias item for each included study.

neither the overall analysis nor the subgroup analysis exhibited difference between the 2 drug regimens (Supplementary Figure 1).

AEs (Safety Population)

In terms of the overall incidence of AEs, there was no significant difference between the 2 groups (5 RCTs, 2215 patients; RD, 0.02; 95% CI, −0.01 to 0.06; I^2 = 0%) (Figure 4A), and the subgroup analysis showed similar results (4 RCTs in the ceftazidime/avibactam subgroup, 1236 patients; RD, 0.03; 95% CI, −0.01 to 0.08; I^2 = 0%; 1 RCT in the ceftolozane/tazobactam subgroup, 979 patients; RD, 0.01; 95% CI, −0.05 to 0.08) (Figure 4A).

However, ceftazidime/avibactam had a significantly higher risk of vomiting compared with meropenem in the subgroup analysis (4 RCTs, 1776 patients; RD, 0.03; 95% CI, 0.01 to 0.05; I^2 = 47%) (Figure 4B). There was no significant difference in diarrhea, headache, cough, or pyrexia between the 2 groups (Supplementary Figure 2).

SAEs (Safety Population)

Five articles consisting of 1897 patients recorded the incidence of SAEs in the safety population. Generally speaking, there was no significant difference between the 2 groups (RD, 0.01; 95% CI, −0.02 to 0.03; I^2 = 28%) (Figure 4C), and there was no difference in the ceftazidime/avibactam subgroup (4 RCTs, 1776 patients; RD, −0.00; 95% CI, −0.02 to 0.02; I^2 = 0%) (Figure 4C). However, 1 article on ceftolozane/tazobactam showed that meropenem had a relatively lower incidence of SAEs (RD, 0.12; 95% CI, 0.01 to 0.23) (Figure 4C).

Mortality (Safety Population)

Four RCTs consisting of 2671 patients reported deaths, and there was no significant difference in mortality between the 2 groups (RD, 0.01; 95% CI, −0.00 to 0.02) (Figure 4D). The same conclusion was found from the subgroup analysis (3 RCTs in the ceftazidime/avibactam subgroup, 1692 patients; RD, 0.01; 95% CI, −0.00 to 0.02; I^2 = 0%; 1 RCT in the ceftolozane/tazobactam subgroup, 979 patients; RD, 0.01; 95% CI, −0.01 to 0.02) (Figure 4D).

DISCUSSION

Antimicrobial therapy is crucial in the progression of cIAIs. The misuse of antibiotic regimens (by administering inappropriate antimicrobial agents, for example) is perhaps the strongest predictor of unsatisfactory treatment outcome. A recent nationwide observational study in Japan showed an association between inadequate antimicrobial therapy and higher mortality rates in patients with sepsis and cIAIs, which can be significantly reduced by taking intra-abdominal cultures [18]. However, delayed use of antibiotics until the results of susceptibility tests are available has also been shown to increase the rate of failure and even increase the risk of mortality [19, 20]. The choice of empirical antimicrobial therapy is complicated, owing to the diverse species that are implicated in cIAIs and the increasing emergence of drug-resistant pathogens.

Patients with severe cIAIs often have 1 or more high risk factors for poor prognosis or drug-resistant bacterial infection. Therefore, broad-spectrum antibiotics should be selected for treatment to minimize the treatment failure caused by inadequate initial treatment. In terms of antibiotic selection, it is usually necessary to select drugs covering gram-negative bacteria, such as *P. aeruginosa* and Enterobacteriales, as well as intestinal *Streptococcus* and most anaerobic bacteria. Labricciosa et al. [21] conducted a secondary analysis from 2 prospective multicenter color surveillance studies using a case–control approach to evaluate the factors associated with the isolation of MDR organisms in cIAIs. They found that MDR organisms represent 9.8% of total isolated micro-organisms, and the overall incidence rate of MDR organisms was 13.9%. MDR organisms are more frequently isolated in patients with HA-cIAIs (25.4%). According to Chinese guidelines for the diagnosis and management of intra-abdominal infection (2019 edition), carbapenem is still the first choice among the commonly used drugs, and

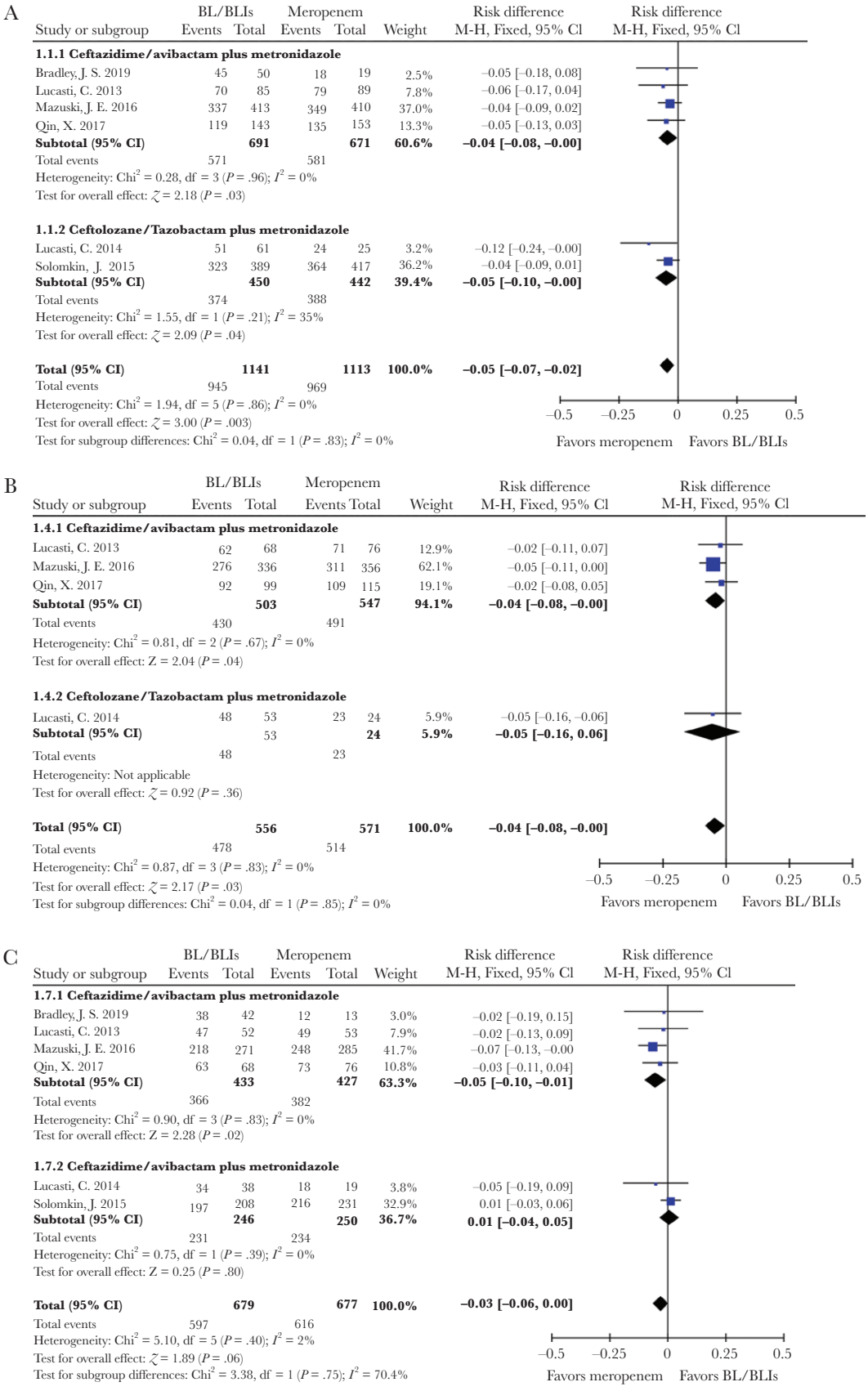

Figure 3. Forest plots showing risk difference with 95% CI of efficacy outcomes. A, Clinical success in mMITT population. B, The rate of overall microbiological success in a fixed-effects model. C, Microbiological success of *E. coli* in a fixed-effects model. "Favors" means higher incidence of efficacy outcomes. Abbreviation: mMITT, microbiologically modified intention-to-treat.

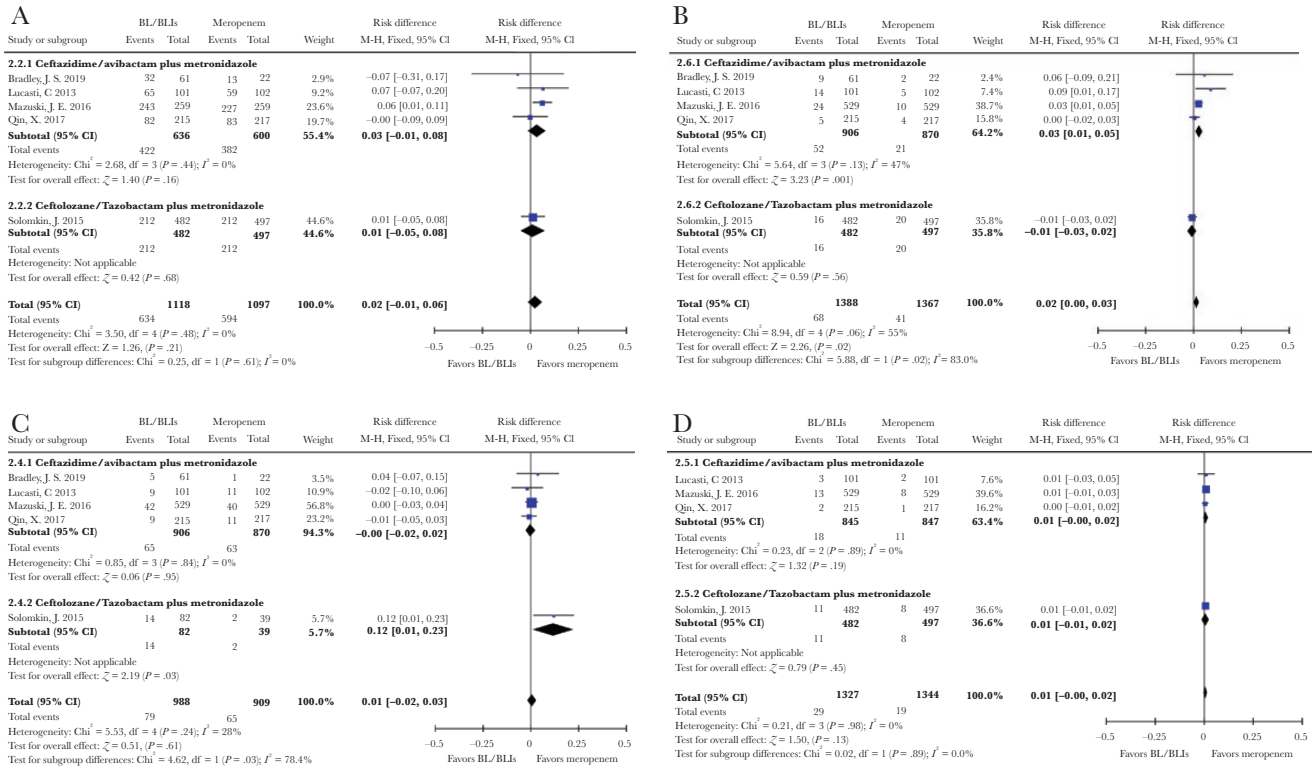

Figure 4. Forest plots showing risk difference with 95% CI of safety outcomes. A, Adverse events. B, Vomiting. C, Serious adverse events. D, Mortality. "Favors" means lower incidence of safety outcomes.

the overall order is set as follows: meropenem > imipenem cilastatin, ertapenem, β-lactamase inhibitor > tigecycline > third-generation cephalosporin plus metronidazole > second-generation cephalosporin plus metronidazole [22]. A large multicenter epidemiology of cIAI treatment in the United States has shown that despite a high prevalence of resistance in third-generation cephalosporins and carbapenems, about one-quarter of all empiric regimens contain a carbapenem, which is a marker for slightly lower postinfection length of stay, but higher costs and risk of hospital complications [23]. Under the pressure of carbapenem overuse and the emergence of resistance, carbapenem-sparing strategies have been implemented. Data regarding application of noncarbapenem β-lactams are urgently need.

Unfortunately, our meta-analysis preliminarily indicated that carbapenem was still irreplaceable in the treatment of cIAIs. The inferiority of BL/BLIs was mainly reflected by the lower clinical, microbiological success rates and higher risk of vomiting.

In terms of microbiological efficacy, ceftolozane/tazobactam and ceftazidime/avibactam have similar spectra of antimicrobial activity, but with some important differences. According to an in vitro activity test against 3269 Enterobacterales isolates from medical centers in the United States, the most active agents against Enterobacterales are ceftazidime/avibactam; meropenem is the second, and ceftolozane/tazobactam is relatively poor [24]. Interestingly, there is an opposite trend with our results, showing that in terms of microbiological response to *E. coli*, ceftolozane/tazobactam is comparable to carbapenem, while ceftazidime/avibactam does not perform as well as carbapenem. However, analysis of *Klebsiella pneumoniae* alone did not show any significant difference, perhaps because of the small number of samples. In addition to Enterobacteriales, *P. aeruginosa* is also a very common pathogen of cIAIs. Buehrle et al. [25] compared the antibacterial activity of ceftolozane/tazobactam and ceftazidime/avibactam against meropenem-resistant *P. aeruginosa* strains. The results showed that ceftolozane/tazobactam has stronger antibacterial activity, and it can continuously inhibit *P. aeruginosa* strains from the respiratory tract, blood, wounds, and other parts as well as other insensitive β-lactam drugs. This may be related to the activity mechanism that ceftolozane is an inhibitor of penicillin-binding proteins (PBPs) of *P. aeruginosa* (eg, PBP1b, PBP1c, and PBP3) and *E. coli* (eg, PBP3) [26]. Results from the China Antimicrobial Surveillance Network (CHINET) in 2017 of the in vitro activities of ceftazidime/avibactam and ceftolozane/tazobactam against clinical isolates also showed that ceftolozane/tazobactam shows a better effect against *P. aeruginosa*. However, this unique advantage of ceftolozane/tazobactam in *P. aeruginosa* was not observed in our analysis. In terms of the microbiological response rate of anaerobes, we

found that the 2 novel BL/BLIs in combination with metronidazole were comparable to carbapenem based on the existing data.

In addition, the results of our analysis were not optimistic in terms of the clinical effectiveness of novel BL/BLIs. Ceftolozane was approved by the FDA in 2014 for use in combination with tazobactam for the treatment of serious infections, such as cIAIs and complicated urinary tract infections (cUTIs) [27]. Ceftazidime/avibactam was approved in 2015 for cIAIs and cUTIs [28]. Kongnakorn et al. developed a sequential, patient-level simulation model to compare the cost-effectiveness of ceftazidime/avibactam, ceftolozane/tazobactam, and meropenem for cIAIs, and they gave a very optimistic evaluation of ceftazidime/avibactam. Ceftazidime/avibactam, compared with ceftolozane/tazobactam and meropenem, has better clinical outcomes in terms of higher cure rate, shorter hospital stays, and increased quality-adjusted life-years (QALY) per patient [29]. In recent years, many research data have also supported that the clinical efficacy of the 2 new drug combinations is comparable to that of meropenem in the treatment of cIAIs [30]. However, based on all the RCT analyses, the clinical efficacy of the new drug is not as good as expected. According to the drug label, the recommended dose of ceftolozone/tazobactam is 1.5 g IV over 1 h, q8h, and the recommended duration is 4–14 days for cIAIs [31]. The recommended dose of ceftazidime/avibactam is 2.5 g IV over 2 hours, q8h, and the cIAI course of treatment is 5–14 days [32]. The recommendation for the flexibility of duration may be attributed to the complexity and variability of cIAIs. At present, BL/BLIs are generally available only as combinations with a fixed dose ratio. For instance, ceftazidime/avibactam formulations are prepared at a ratio of 4:1 (ceftazidime to avibactam), and ceftolozone/tazobactam formulations are prepared at a ratio of 2:1 (ceftolozane to tazobactam). In some inevitably clinical scenarios (eg, severe [high inoculum] infections), the present ratio of BL/BLIs cannot provide adequate inhibitor exposures. However, it is impossible to change the administration ratio flexibly in clinical practice [33]. Previous studies on the pharmacokinetics of tazobactam in patients undergoing elective colorectal surgery have shown that the mean concentration of tazobactam in gastrointestinal tissues (appendix, proximal, and distal mucosa) exceeds its levels in plasma after 1 hour [34]. At present, due to the lack of clinical application, very few typical case reports or clinical studies have been published. Research on tissue penetrability and distribution for these new agents is still limited, which is very important and directly affects the efficacy of beta-lactamase inhibitors in the setting of the hostile environment of the infected abdomen. Furthermore, there are few guidelines and suggestions on the clinical application of 2 novel BL/BLIs. Testing for susceptibility to ceftolozane/tazobactam or ceftazidime/avibactam is advised for patients as definitive therapy in the setting of confirmed resistance to other β-lactam agents. For isolates remaining sensitive to carbapenems, ceftolozane/tazobactam or ceftazidime/avibactam may only be considered as carbapenem-sparing options at select institutions with increasing reports of carbapenem resistance [35]. Obviously, despite the rapid development of antibiotic drugs, the era of new antibiotics has not come before more clinical studies prove their safety and efficacy.

In terms of safety, the most frequently reported AEs in both groups were nausea, vomiting, and diarrhea, and these are expected events in a postoperative population with cIAI. Our results concluded that novel BL/BLIs in combination with metronidazole showed noninferiority compared with meropenem, and there were no more safety-related events in terms of overall AEs, SAEs, or mortality in the treatment of cIAIs. Previous meta-analyses have proven that ceftazidime/avibactam and ceftolozane/tazobactam exhibit comparable safety with alternative antibiotics in the treatment of gram-negative bacterial infections [36, 37]. However, our study showed that ceftazidime/avibactam had a higher incidence of certain AEs, such as vomiting, compared with meropenem. Therefore, more real-world studies are needed to discuss its safety.

Li et al. [38] reported that the efficacy and safety of BL/BLI monotherapy or combination therapy are similar or even better than those of carbapenem. The difference in results was mainly due to the following: First, we included more recent RCTs than before. Second, previous studies considered the clinical success rate in the ME population to be the microbiological success rate, while our study only included clear microbiological success data for statistical analysis. Finally, with respect to clinical success, Li et al. [38] chose a CE population for analysis, while our study chose an mMITT population to reduce the bias caused by no treatment or loss to follow-up after treatment.

There are several limitations to the present research. First, all the RCTs included in this article were sponsored by pharmaceutical groups and had a high reporting bias. More high-quality postmarketing evaluation is still required. Second, there are no clinical studies directly comparing the safety and effectiveness of ceftolozane/tazobactam and ceftazidime/avibactam in the treatment of cIAIs. Therefore, it is difficult to evaluate the superiority and inferiority of these 2 BL/BLIs. Meanwhile, only meropenem was applied in the present meta-analysis, so we lacked data on other carbapenems. Last, despite their recent introduction into clinical practice, clinical reports of resistance to novel BL/BLIs among typically susceptible organisms have already emerged, in some cases associated with therapeutic failure. Awareness of the potential for resistance, early detection, and dose optimization may be important in preserving the utility of these agents [39].

In conclusion, the combination regime of novel BL/BLIs and metronidazole for cIAIs was less effective than meropenem. It is necessary to carefully consider the feasibility of replacing

meropenem as the primary agent in new drug combinations in the clinical practice of cIAIs.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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