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Novel β-Lactam/β-Lactamase inhibitor combinations vs alternative antibiotics in the treatment of complicated urinary tract infections

A meta-analysis of randomized controlled trials

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Abstract

Objectives: This meta-analysis assessed the efficacy and safety of novel β-lactam/β-lactamase inhibitor combinations in the treatment of complicated urinary tract infection (cUTI)/acute pyelonephritis (APN).

Methods: PubMed, Web of Science, EBSCO (Elton B. Stephens Co.), Cochrane Library, Ovid MEDLINE, and Embase databases were accessed until November 21, 2019. In this meta-analysis, only randomized controlled trials comparing the treatment efficacy of novel β-lactam/β-lactamase inhibitor combinations with other antibiotics for cUTI/APN in adult patients were included. The outcomes included the clinical and microbiological responses, and risk of adverse events (AEs).

Results: Overall, the experimental group treated with a novel β-lactam/β-lactamase inhibitor combination and the control group comprised 1346 and 1376 patients, respectively. No significant difference in the clinical response rate at test-of-cure was observed between the novel β-lactam/β-lactamase inhibitor combination and comparators among the microbiological modified intent-to-treat population (89.1% vs 88.3%, OR, 1.04; 95% confidence interval [CI], 0.76–1.42; $I^2=28\%$) and the microbiologically evaluable population (95.2% vs 94.7%, OR, 1.12; 95% CI, 0.68–1.84; $I^2=0\%$). Additionally, the novel β-lactam/β-lactamase inhibitor combination was associated with a better microbiological response at test-of-cure than the comparators among the microbiological modified intent-to-treat population (74.4% vs 68.5%, OR, 1.34; 95% CI, 1.04–1.72; $I^2=45\%$) and microbiologically evaluable population (80.1% vs 72.5%, OR, 1.49; 95% CI, 1.06–2.10; $I^2=58\%$). Finally, the risk of AEs associated with the novel β-lactam/β-lactamase inhibitor combination was similar to that associated with the comparators (treatment-emergent adverse events [TEAE], OR, 1.04; 95% CI, 0.87–1.23; $I^2=19\%$; serious AEs, OR, 1.21; 95% CI, 0.82–1.76; $I^2=0\%$; treatment discontinuation for drug-related TEAE, OR, 077; 95% CI, 0.38–1.56, $I^2=5\%$). The all-cause mortality did not differ between the novel β-lactam/β-lactamase inhibitor combination and comparators (OR, 1.19; 95% CI, 0.37–3.81; $I^2=0\%$).

Conclusions: The clinical and microbiological responses of novel β-lactam/β-lactamase inhibitor combinations in the treatment of cUTI/APN are similar to those of other available antibiotics. These combinations also share a safety profile similar to that of other antibiotics.

Abbreviations: AE = adverse event, APN = acute pyelonephritis, CE = clinically evaluable, cUTI = complicated urinary tract infection, ME = microbiologically evaluable, MITT = modified intention-to-treat, mMITT = microbiological modified intention-to-treat, RCT = randomized controlled trial, TEAE = treatment-emergent adverse event, TOC = test-of-cure.

Keywords: carbapenem, complicated urinary tract infection, eravacycline, novel β-lactam antibiotics and β-lactamase inhibitors

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All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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1. Introduction

Complicated urinary tract infection (cUTI) and acute pyelonephritis (APN) are common infections and could be associated with considerable morbidity and mortality. Prompt use of appropriate antibiotics is essential for the successful management of cUTI/APN.[1] However, the emergence and dissemination of antibiotics resistance among commonly encountered bacteria in cUTI/APN have largely limited the therapeutic options.[2–4] Therefore, search for new antimicrobials to combat cUTI/APN caused by antibiotic-resistant bacteria is required.

Recently, several novel β-lactam/β-lactamase inhibitor combinations, including ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem-cilastatin/relebactam, aztreonam/avibactam, cefepime/tazobactam, ceftaroline/avibactam, cefepime/zidebactam, and meropenem/nacubactam, have been developed. Some of these combinations such as ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, and imipenem-cilastatin/relebactam have been approved by the Food and Drug Administration for clinical use.[5–10] These new β-lactam/β-lactamase inhibitor combinations retain activity against a broad spectrum of bacteria, including the most commonly encountered gram-negative bacteria causing cUTI/APN. Moreover, they exhibit potent in vitro activity against many multidrug-resistant organisms.[11–14] Since their development, the clinical efficacy and safety of ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, and imipenem-cilastatin/relebactam in cUTI/APN treatment have been evaluated in several clinical studies.[15–20] However, updated evidence regarding the efficacy and safety of novel β-lactam/β-lactamase inhibitor combinations in cUTI/APN treatment is required. Therefore, we conducted this meta-analysis to provide real-time evidence on the efficacy and safety of β-lactam/β-lactamase inhibitor combinations in the treatment of adult patients with cUTI/APN.

2. Methods

2.1. Study search and selection

All randomized controlled trials (RCTs) were identified through a systematic review of the literature in PubMed, Web of Science, EBSCO (Elton B. Stephens Co.), Cochrane databases, Ovid MEDLINE, and Embas until November 21, 2019 using the following search terms: "ceftazidime/avibactam," "avycaz," "zavicefta," "ceftolozane/tazobactam," "zerbaxa," "meropenem/vaborbactam," "vabomere," "vaborem," "imipenem/cilastatin/relebactam," "imipenem/relebactam," "recarbrio," "cefepime/tazobactam," "aztreonam/avibactam," "ceftaroline/avibactam," "cefepime/zidebactam," "WCK 5222," and "Meropenem/nacubactam." Only RCTs that directly compared the clinical efficacy and safety of novel β-lactam/β-lactamase inhibitor combinations with other antimicrobial agents in the treatment of adult patients with cUTI/APN were included. Studies that only reported *in vitro* activity, animal studies, and pharmacokinetic–pharmacodynamic assessment were excluded. Two of the authors (Chang and Lan) searched and examined publications independently. A third author (Lai) offered resolution in case of a disagreement. The following data were extracted: year of publication, study design, antimicrobial regimens, clinical and microbiological outcomes, and the risk of adverse event (AEs). This systematic review and meta-analysis were conducted according to the preferred reporting items for systematic reviews and meta-analyses statement

2.2. Outcome measurement

The outcomes of this meta-analysis included clinical and microbiological responses assessed at the test-of-cure (TOC) and end-of-treatment (EOT) visits in the microbiological modified intent-to-treat (mMITT), clinically evaluable (CE), and microbiologically evaluable (ME) populations. The modified intention-to-treat (MITT) population included all intent-to-treat patients who received any amount of the study drug, and the mMITT population included all MITT patients who met the minimal disease definition of clinical infection and had the baseline pathogen identified. The CE population included all MITT patients who met the minimal disease definition of acute bacterial infection and had a clinical response assessed at the TOC visit. The ME population included all CE patients in whom a baseline pathogen had been identified and a microbiological response had been assessed. Additionally, the risk of AEs was measured through safety outcome analysis.

2.3. Data analysis

The Cochrane risk-of-bias tool[21] was used to assess the quality of the included RCTs and associated risk of bias. The software Review Manager, version 5.3. with the random-effects model was used for statistical analyses. Pooled odds ratio (OR) and 95% confidence intervals (CIs) were calculated for outcome analyses.

3. Results

3.1. Study selection

The search results yielded a total of 1011 studies from the online databases and 558 studies were excluded on account of duplication. The remaining 453 article were identified from PubMed (n = 153), Ovid MEDLINE (n = 114), Cochrane library (n = 36), Web of Science (n = 295), Embase (n = 247), and EBSCO (n = 56). Moreover, 434 studies were found to be irrelevant after the title and abstract were screened, and 13 studies were found to be irrelevant after the full text was screened. Eventually, 6

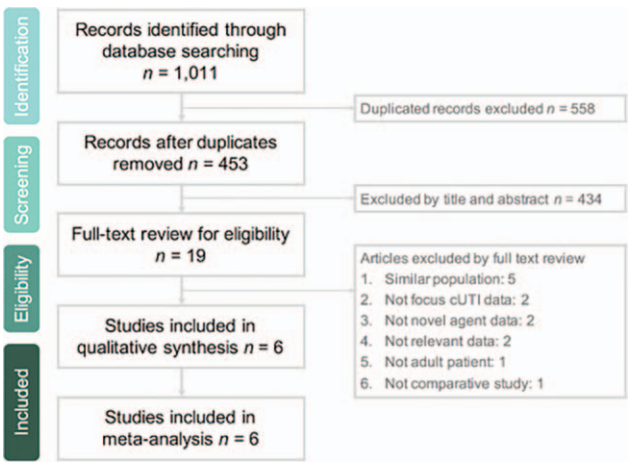

Figure 1. The flow chart for study selection.

Table 1

Characteristics of included studies.

Study, published year	Study design	Study duration	No of patients		Dose regimen	
			Study	Control	Study	Control
Vazquez et al, 2012	Prospective randomized, investigator-blinded, multinational, phase 2 trial	2008–2010	68 (APN: 44, cUTI without APN: 24)	67 (APN: 41, cUTI without APN: 26)	ceftazidime-avibactam (500 mg/125 mg) every 8 h	imipenem–cilastatin 500 mg iv (30-min infusion) every 6 h
Wagenlehner et al, 2015	randomized, double-blind, multinational, multicenter, phase 3 trial	2011–2013	398 (APN: 328, cUTI without APN: 70)	402 (APN: 328, cUTI without APN: 74)	ceftolozane-tazobactam (1000 mg/500 mg) every 8 h	Levofloxacin 750 mg everyday
Wagenlehner et al, 2016	randomized, multinational, multicenter, double-blind, phase 3 trials	2012–2014	393 (APN: 287, cUTI without APN: 106)	417 (APN: 296, cUTI without APN: 121)	ceftazidime-avibactam; 2000 mg/500 mg every 8 h	doripenem 500 mg every 8 h
Carmeli et al, 2016	pathogen-directed, multinational, randomized, open-label, phase 3 trial	2013–2014	144 (APN: 57, cUTI without APN: 87)	137 (APN: 70, cUTI without APN: 67)	ceftazidime-avibactam (2000 mg/500 mg) every 8 h	Best available therapy
Sims et al, 2017	multinational, randomized clinical, phase 2b trial	2012–2015	71 (APN: 35, cUTI without APN: 36)	80 (APN: 37, cUTI without APN: 43)	Imipenem/relebactam (500 mg/250 mg) every 6 h	Imipenem-cilastatin 500 mg every 6 h
Kaye et al, 2018	multinational, randomized clinical, phase 3 trial	2014–2016	272 (APN: 161, cUTI without APN: 111)	273 (APN:161, cUTI without APN: 112)	meropenem-vaborbactam (2 g/2 g) every 8 h	piperacillin-tazobactam (4 g/0.5 g) every 8 h

Study, published year	Mean age (±SD) or median (range) yrs		Age ≥ 65 yrs, n (%)		Male sex (%)		Bacteremia, n (%)	
	Study	Control	Study	Control	Study	Control	Study	Control
Vazquez et al, 2012	46.4 (18.2)	48.2 (18.4)	11 (16.2)	12 (17.9)	17 (25)	18 (26.9)	3 (4.4)	4 (6.0)
Wagenlehner, et al, 2015	49.1 (19.7)	48.1 (20.2)	100 (25.1)	99 (24.6)	159 (29.8)	155 (29.0)	29 (7.3)	33 (8.2)
Wagenlehner et al, 2016	51.4 (20.2)	53.3 (18.6)	NA	NA	121 (30.8)	124 (29.7)	38 (9.7)	33 (7.9)
Carmeli et al, 2016	64.3 (14.6)	61.3 (15.3)	NA	NA	80 (56)	74 (54)	4 (3)	6 (4)
Sims et al, 2017	58 (18–90)	61 (18–86)	25 (35.2)	35 (43.8)	33 (46.5)	44 (55)	NA	NA
Kaye et al, 2018	53.0 (19.4)	52.6 (20.9)	87 (32.0)	103 (37.7)	91 (33.5)	93 (34.1)	NA	NA

APN = acute pyelonephritis, cUTI = complicated urinary tract infection, NA = not applicable.

RCTs[15–20] were included in this meta-analysis (Fig. 1, Appendix 1, http://links.lww.com/MD/E118).

3.2. Study characteristics

The 6 RCTs[15–20] included were multicenter and multinational studies (Table 1). Two[15,19] were phase II studies and the other 4[16–18,20] were phase III studies. Three studies evaluated the use of ceftazidime/avibactam,[15,17,18] and the remaining 3 studies investigated the use of ceftolozane/tazobactam,[16] meropenem/vaborbactam,[20] and imipenem-cilastatin/relebactam[19] each. Overall, the experimental group treated with the novel β-lactam/β-lactamase inhibitor combination and the control group comprised 1346 (APN, n=912 and cUTI without APN, n=434) and 1376 patients (APN, n=933 and cUTI without APN, n=443), respectively. The mean patient age in the experimental and control groups was 52.5 and 52.6 years, respectively. Additionally, 30.4% and 30.2% of patients in the experimental and control groups were men. Only less than 10% of the patients had concomitant bacteremia. Table 2 summarizes the common pathogens in this meta-analysis. *Escherichia coli* was the most common organism, followed by *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (Table 2). Almost all risks-of-bias in each study were low. Except et Carmeli al's study[18] had high risk of selection, performance and detection bias, most of the other study had low risk of bias in all fields. The publication bias was shown in funnel plot (Fig. 2).

3.3. Clinical efficacy

In the pooled analysis of 6 RCTs, no significant difference was observed in the clinical response rate at TOC in the mMITT

Table 2

Common pathogen.

Study, published year	*E. coli*		*K. pneumoniae*		P. aeruginosa		*Proteus mirabilis*		*Enterobacter cloacae*	
	Study	Control	Study	Control	Study	Control	Study	Control	Study	Control
Vazquez et al, 2012	25	33	0	0	2	0	0	1	0	1
Wagenlehner, et al, 2015	262	284	25	23	7	12	10	11	6	7
Wagenlehner et al, 2016	292	306	44	56	18	20	17	13	11	13
Carmeli et al, 2016	59	57	55	65	14	5	0	0	8	6
Sims et al, 2017	46	47	8	15	5	5	3	5	4	3
Kaye et al, 2018	125	117	30	28	0	0	6	12	10	5
All	809	844	162	187	46	42	36	42	39	35

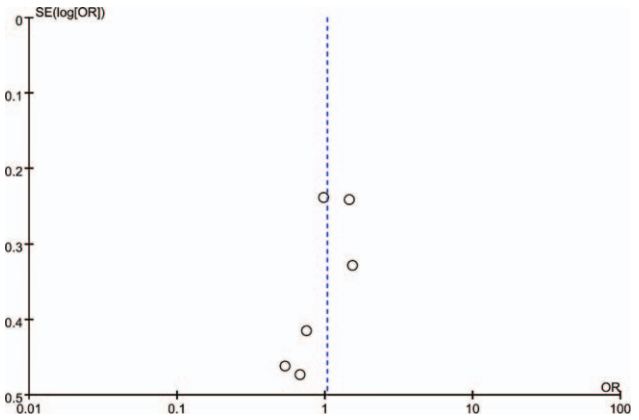

Figure 2. Funnel plot for comparison.

population between the novel β-lactam/β-lactamase inhibitor combination and comparators (89.1% vs 88.3%, OR, 1.04; 95% CI, 0.76–1.42; $I^2=28\%$, Fig. 3).[15–20] Four RCTs[17–20] reported the clinical outcome in the ME population, and no significant difference was observed in the clinical response at TOC (95.2% vs 94.7%, OR, 1.12; 95% CI, 0.68–1.84; $I^2=0\%$). Similarly, no significant difference was observed in the clinical response at EOT between the novel β-lactam/β-lactamase inhibitor combination and comparators in the mMITT population (95.4% vs 96.2%, OR, 0.82; 95% CI, 0.50–1.35; $I^2=0\%$) and ME population (96.9% vs 96.7%, OR, 0.88; 95% CI, 0.39–2.00; $I^2=50\%$)

In the pooled analysis of the three studies[15,17,18] comparing ceftazidime/avibactam and other antibiotics, no significant difference was observed in the clinical response rate at TOC in the mMITT population (87.7% vs 88.7%, OR, 0.88; 95% CI, 0.61–1.28; $I^2=0\%$) and ME population (97.3% vs 96.5%, OR, 1.31; 95% CI, 0.59–2.90; $I^2=0\%$). Additionally, no significant difference was observed in the clinical response rate at EOT in the mMITT population (96.8% vs 98.0%, OR, 0.61; 95% CI, 0.28–1.31; $I^2=71\%$) and ME population (98.1% vs 99.4%, OR, 0.30; 95% CI, 0.08–1.10) between ceftazidime/avibactam and other antibiotics.

In the pooled analysis of the two studies[19,20] comparing carbapenem/β-lactamase inhibitor combination and other antibiotics, no significant difference was observed in the clinical response rate at TOC in the mMITT population (88.0% vs 87.1%, OR, 0.95; 95% CI, 0.34–2.67; $I^2=71\%$) and ME population (91.5% vs 91.3%, OR, 1.01; 95% CI, 0.53–1.90; $I^2=0\%$). Additionally, no significant difference was observed in the clinical response rate at EOT in the mMITT population (92.5% vs 92.4%, OR, 1.01; 95% CI, 0.53–1.94; $I^2=0\%$) and ME population (95.9% vs 96.3%, OR, 0.93; 95% CI, 0.37–2.35; $I^2=0\%$) between the carbapenem/β-lactamase inhibitor combination and other antibiotics.

3.4. Microbiological response

In the pooled analysis of six RCTs,[15–20] the novel β-lactam/β-lactamase inhibitor combination was associated with a better microbiological response at TOC than the comparators in the mMITT population (74.4% vs 68.5%, OR, 1.34; 95% CI, 1.04–1.72; $I^2=45\%$, Fig. 4). A similar trend was observed in the ME

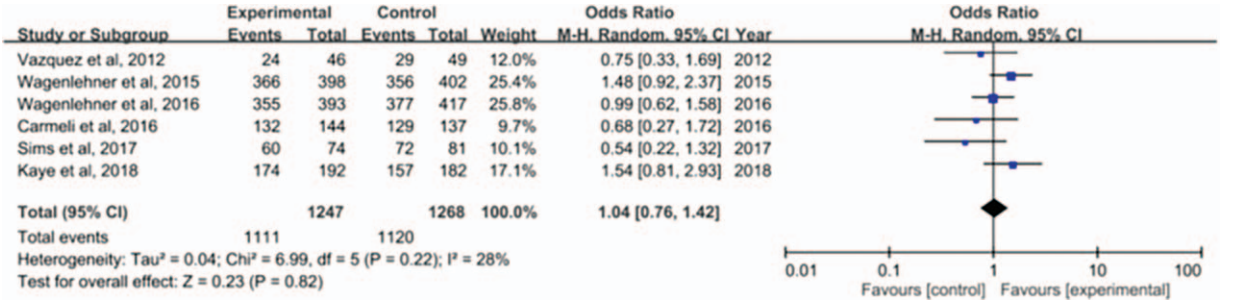

Figure 3. Forest plot of the clinical response rate at the test-of-cure visit among microbiological modified intent-to-treat populations.

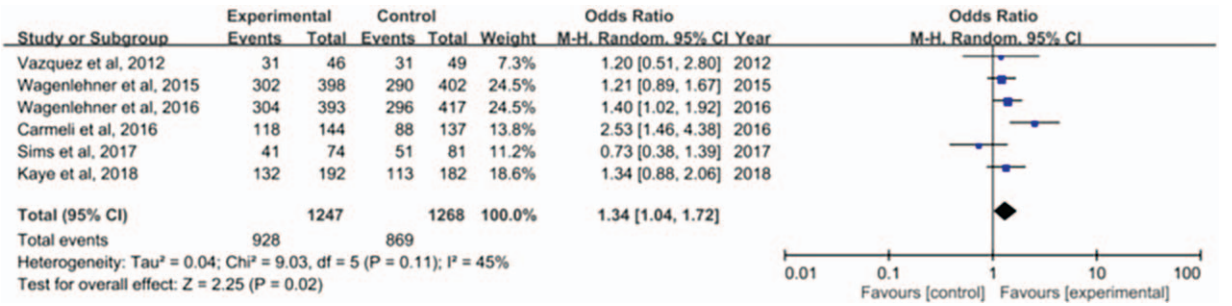

Figure 4. Forest plot of the microbiological response rate at the test-of-cure visit among microbiological modified intent-to-treat populations.

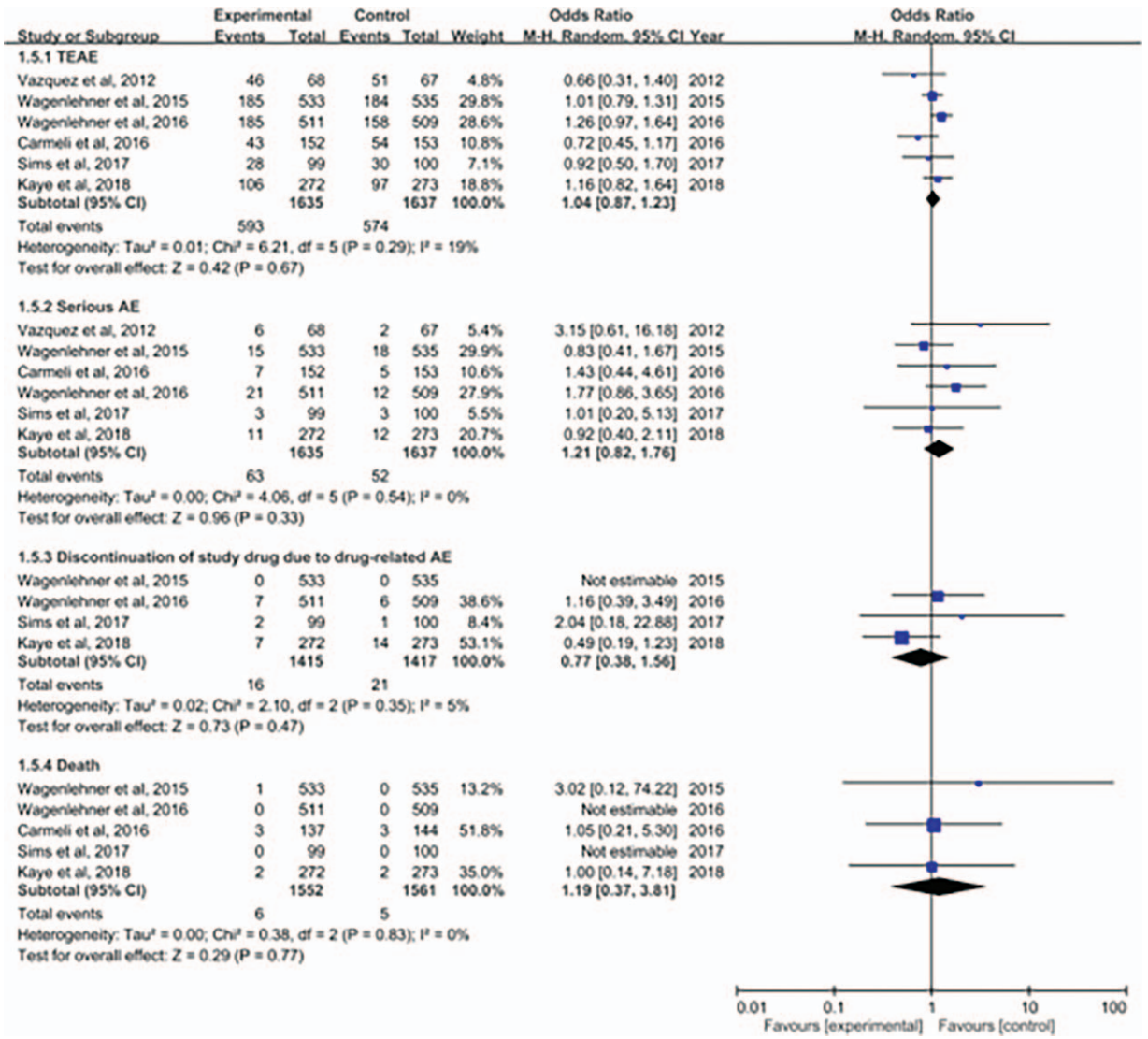

Figure 5. Forest plot of risks of treatment-emergent adverse events, serious AE, discontinuation of treatment due to drug-related AE, and all-cause mortality. AE = adverse events.

population (80.1% vs 72.5%, OR, 1.49; 95% CI, 1.06–2.10; $I^2=58\%$). For *E coli*, the novel β-lactam/β-lactamase inhibitor combination demonstrated a better microbiological response at TOC than the comparators in the ME population (85.0% vs 75.9%, OR, 1.87; 95% CI, 1.21–2.90; $I^2=50\%$). A similar trend was observed for *K. pneumoniae* (79.7% vs 65.1%, OR, 2.20; 95% CI, 1.28–3.79; $I^2=0\%$).

3.5. Risk of AEs

Overall, the novel β-lactam/β-lactamase inhibitor combination was associated with a risk of AEs similar to the comparators (TEAE, OR, 1.04; 95% CI, 0.87–1.23; $I^2=19\%$; serious AEs, OR, 1.21; 95% CI, 0.82–1.76; $I^2=0\%$; treatment discontinuation for drug-related TEAE, OR, 077; 95% CI, 0.38–1.56, $I^2=5\%$, Fig. 5). The all-cause mortality did not differ between the novel β-lactam/β-lactamase inhibitor combination and comparators (OR, 1.19; 95% CI, 0.37–3.81; $I^2=0\%$). Regarding common AEs, no significant difference was observed between the novel β-lactam/β-lactamase inhibitor combination and comparators for nausea (OR, 1.24; 95% CI, 0.79–1.95; $I^2=0\%$), diarrhea (OR, 0.80; 95% CI, 045–1.43; $I^2=46\%$), and headache (OR, 0.99; 95% CI, 0.58–1.67; $I^2=64\%$).

4. Discussion

This meta-analysis included 6 RCTs with 2722 patients to compare the efficacy and safety of the novel β-lactam/β-lactamase inhibitor combinations, namely ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, and imipenem-cilastatin/relebactam, with other antibiotic regimens for the treatment of cUTI/APN. In this study, we demonstrated that the novel β-lactam/β-lactamase inhibitor combinations could achieve a clinical response similar to that of other comparators, and this significant finding was supported by the following evidence. First, the pooled analysis of six studies[15–20] revealed that the clinical response rate of the novel β-lactam/β-lactamase inhibitor combinations was similar to that of the

other comparative antibiotics in various populations(ie, mMITT and ME) and at different timings of the assessment—TOC and EOT. Second, subgroup analysis of the three studies on ceftazidime/avibactam,[15,17,18] revealed that ceftazidime/avibactam had a clinical efficacy similar to that of the comparators. Third, subgroup analysis of 2 studies[19,20] revealed that the clinical efficacy of the novel carbapenem/β-lactamase inhibitor combinations—meropenem/vaborbactam and imipenem-cilastatin/relebactam, was similar to that of the comparators. In summary, all these findings indicated that novel β-lactam/β-lactamase inhibitor combinations including ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, and imipenem-cilastatin/relebactam can be as effective as other antibiotics in the treatment of cUTI/APN.

In addition to the clinical response, this meta-analysis demonstrated that the microbiological response rate of the novel β-lactam/β-lactamase inhibitor combinations was comparable to that of the comparators. This noninferiority in terms of microbiological responses between the novel β-lactam/β-lactamase inhibitor combinations and comparators was observed in the analysis of both mMITT and ME populations and two common pathogens—*E coli* and *K pneumoniae*. These findings regarding the favorable microbiological response of the novel β-lactam/β-lactamase inhibitor combination are supported by many *in vitro* studies.[2,22–24] For ceftazidime/avibactam, the MIC_{90} value against the most common Enterobacteriaceae was 0.25 mg/L for *E coli*, 1 mg/L for *K pneumoniae*, 0.06 mg/L for *P mirabilis*, and 2 mg/L for *Enterobacter cloacae*.[22] Based on a surveillance in the USA and European medical centers, ceftolozane/tazobactam demonstrated potent in vitro activity when tested against gram-negative pathogens causing UTI, including *E coli* and *K pneumoniae*.[23] The potent in vitro activity of meropenem/vaborbactam and imipenem-cilastatin/relebactam against Enterobacteriaceae and *P aeruginosa* has been reported in studies.[2,24] Thus, these findings regarding the microbiological response in this meta-analysis and the in vitro activity in previous studies support the use of novel β-lactam/β-lactamase inhibitor combinations for cUTI/APN.

Finally, this meta-analysis assessed the risk of AEs associated with novel β-lactam/β-lactamase inhibitor combinations. The novel β-lactam/β-lactamase inhibitor combinations had a risk of AEs (ie, TEAE, serious AE, treatment discontinuation due to TEAE, and all-cause mortality) similar to other antibiotics. For other common AEs, including nausea, diarrhea, and headache, no significant difference was observed between the novel β-lactam/β-lactamase inhibitor combinations and other antibiotics. Thus, these findings remind clinicians that novel β-lactam/β-lactamase inhibitor combinations are as tolerable as other antibiotics.

This meta-analysis had one major limitation. These novel β-lactam/β-lactamase inhibitor combinations should be used for treating multidrug-resistant organism (MDRO)-associated infections. However, we could not assess the association between in vitro activity and clinical response for each specific pathogen, particularly for MDROs, due to lack of data. This deficit could be partially compensated by the results of many in vitro studies[11,25–27] that demonstrated the potent in vitro activity of novel β-lactam/β-lactamase inhibitor combinations against MDROs.

In conclusion, the clinical and microbiological responses of novel β-lactam/β-lactamase inhibitor combinations in the treatment of cUTI/APN are similar to those of other available antibiotics. Additionally, these combinations share a safety profile similar to that of other antibiotics.

Author contributions

Conceptualization: Li-Chin Lu, Chih-Cheng Lai, Shao-Huan Lan, Shun-Hsing Hung, Wei-Ting Lin.
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Supervision: Shun-Hsing Hung, Wei-Ting Lin.
Writing – original draft: Chih-Cheng Lai.
Writing – review & editing: Shun-Hsing Hung, Wei-Ting Lin.

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