Am J Transl Res 2025;17(8):6488-6503
www.ajtr.org /ISSN:1943-8141/AJTR0166027

Review Article

The role of β-lactam/β-lactamase inhibitor combinations in multidrug-resistant bacterial infections: a comprehensive meta-analysis

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Received May 14, 2025; Accepted June 27, 2025; Epub August 15, 2025; Published August 30, 2025

Abstract: Background: Multidrug-resistant (MDR) bacterial infections pose a global public health challenge. β-Lactam/β-lactamase inhibitor combinations (BLIs) are essential for treating MDR infections, although their efficacy varies across studies. This meta-analysis aims to evaluate their clinical value. Methods: A systematic search of PubMed, Embase, and Cochrane Library was conducted for randomized controlled trials (RCTs) on BLIs for MDR bacterial infections published from January 2000 to December 2024. Study quality was assessed using the Cochrane Risk of Bias tool, and meta-analysis was performed using RevMan 5.4. Primary outcomes included clinical efficacy rate, bacterial clearance rate, and incidence of adverse reactions. Results: Eighteen high-quality RCTs involving 2,356 patients were included. BLIs showed a significantly higher clinical efficacy rate (76.23%) than controls (62.45%) (RR=1.59, 95% CI: 1.44-1.73, P<0.001) and bacterial clearance rate (71.58% vs. 58.67%, RR=1.21, 95% CI: 1.16-1.26, P<0.001). Subgroup analysis revealed clinical efficacy rates of 73.45% for carbapenem-resistant Enterobacteriaceae (CRE) and 78.32% for ESBL-producing Enterobacteriaceae, with bacterial clearance rates of 68.72% and 74.11%, respectively. The adverse reaction rate in the BLI group was 15.68% (mainly diarrhea, nausea, rash), which was not significantly different from the control group (17.89%, RR=0.96, 95% CI: 0.85-1.07, P=0.977). Conclusion: BLIs demonstrate high efficacy, bacterial clearance, and safety in treating MDR infections, particularly CRE and ESBL infections. Larger multicenter RCTs are needed for further validation.

Keywords: β-lactam/β-lactamase inhibitor combinations, multidrug-resistant bacterial infection, randomized controlled trial, meta-analysis, clinical efficacy

Introduction

Multidrug Resistance (MDR) bacterial infections have become a severe challenge to global public health and pose a significant threat to human health [1]. The widespread use of antibacterial drugs in clinical, agricultural, and animal husbandry settings has exacerbated the issue of bacterial drug resistance. Emerging drug-resistant strains and increasingly complex resistance mechanisms pose significant challenges [2]. MDR bacteria exhibit resistance to multiple classes of antibacterial drugs, reducing the efficacy of traditional treatment or rendering them ineffective, which escalates treatment complexity and mortality rates for infected patients [3]. Among various drug-resistant pathogens, Gram-negative bacteria pose particularly significant resistance issues. Carbapenem-resistant Enterobacteriaceae (CRE) and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae are inherently resistant to commonly used β-lactam antibiotics, creating substantial challenges for clinical management [4, 5]. CRE synthesize carbapenemase enzymes that hydrolyze carbapenem antibiotics, neutralizing their bactericidal activity. Conversely, ESBL-producing strains degrade diverse β-lactam antibiotics, including penicillins and cephalosporins, severely restricting therapeutic options [6, 7]. Epidemiological data indicate that CRE infections are associated with

https://doi.org/10.62347/JVJW7760

mortality rates significantly higher than those of non-resistant bacterial infections, prolonged hospital stays, and increased healthcare costs [8]. The rising annual incidence of CRE infections in certain healthcare settings further intensifies challenges in infection control and clinical care [9].

β-Lactam antibiotics remain among the most clinically utilized antibacterial agents due to their broad spectrum and potent bactericidal properties [10]. However, bacterial production of β-lactamases that hydrolyze the β-lactam ring structure of these drugs is a primary resistance mechanism, compromising their antimicrobial efficacy [11]. To address this, the combination of β-lactam/β-lactamase inhibitors have emerged. While β-lactamase inhibitors themselves have relatively weak antibacterial activity, they bind tightly to β-lactamase, inhibiting their activity and thereby protecting β-lactam antibiotics from hydrolysis, restoring their antibacterial effect [12]. Common combinations of β-lactam/β-lactamase inhibitors include amoxicillin/clavulanic acid, piperacillin/tazobactam, and cefoperazone/sulbactam. These combinations are widely used in the clinical treatment of drug-resistant bacterial infections [13].

Although the combination of β-lactam/β-lactamase inhibitors holds significant theoretical clinical value, the reported efficacy in treating multidrug-resistant bacterial infections varies across studies [14]. Several investigations have demonstrated the combination's efficacy in treating specific drug-resistant bacterial infections, effectively eradicating pathogens and alleviating patient symptoms. However, other studies report suboptimal therapeutic outcomes, potentially due to factors such as study design, sample size, and characteristics of the infecting strain [15]. This variability in results creates ambiguity for clinicians during treatment selection, hindering evidence-based decision-making due to inconsistent research findings.

To clarify the clinical utility of β-lactam/β-lactamase inhibitor combinations against MDR bacterial infections, a comprehensive synthesis of available research is essential. Meta-analysis, a systematic review methodology, integrates results from multiple independent studies to enhance the reliability and validity of conclusions. By thoroughly reviewing the literature, identifying high-quality randomized controlled trials (RCTs), and applying rigorous quality assessment tools with meta-statistical techniques, this approach enables precise evaluation of the combination's efficacy and safety, offering robust evidence for clinical practice. Clarifying the role of these combinations in managing multidrug-resistant infections will offer clinicians robust support for treatment planning, ultimately improving therapeutic standards and patient outcomes.

Methods

Literature retrieval strategy

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and structured around the PICO framework (Population: MDR-infected patients; Intervention: BLIs; Comparison: other antimicrobial regimens or placebo; Outcome: clinical efficacy, bacterial clearance, adverse events). This study is registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD420250000112.

A systematic literature search was performed in the PubMed, Embase and Cochrane Library databases. These databases are widely recognized for their comprehensive and high-quality research resources, ensuring the completeness and accuracy of the retrieved results. The search time was limited to studies published from January 2000 to December 2024. The retrieval strategy combined both subject terms and free terms. Key subject terms included "β-lactam/β-lactamase inhibitor combination", "multidrug-resistant bacterial infection", and "randomized controlled trial". Supplementary searches were conducted using free terms to enhance the sensitivity and specificity of the search. The search strategy for the PubMed database is as follows: ("β-lactam/β-lactamase inhibitor combinations" [MeSH Terms] OR "β-lactam/β-lactamase inhibitor combinations" [Text Word]) AND ("multidrug - resistant bacterial infections" [MeSH Terms] OR "multidrug resistant bacteria infections" [Text Word]) AND ("randomized controlled trial" [Publication Type] OR "randomized controlled trials" [Text Word]) AND ("2000/01/01" [Date - Publication]: "2024/12/31" [Date - Publication]).

Literature screening

Inclusion criteria: 1) Randomized controlled trial (RCT); 2) The research subjects were patients diagnosed with MDR bacterial infections; 3) Intervention measures: the experimental group was treated with a combination of β-lactam/β-lactamase inhibitors, while the control group was treated with other antibacterial treatment regimens or placebos; 4) The outcome indicators included clinical effective rate, bacterial clearance rate, and incidence of adverse reactions.

Exclusion criteria: 1) Non-randomized controlled trials, cohort studies, case-control studies, etc. 2) Repeatedly published literature with incomplete data or where valid information cannot be extracted; 3) Literature involving animal experiments or *in vitro* experiments.

Screening process

Initially, we reviewed the titles and abstracts to exclude the literature that obviously did not meet the inclusion criteria. Then, full-text reading was conducted for the literature that appeared to meet the criteria, to further determine its eligibility. In case of disagreement, any discrepancies were resolved through discussion or consultation with a third expert.

Data extraction

Data were independently extracted from the included literature. The basic information extracted included the first author, publication year, and research location. The characteristics of the research subjects were documented, including sample size, age, gender, infection site, types of MDR bacteria. Detailed information on the intervention measures included the specific drug names, dosages, administration routes, and treatment courses for the combination of β-lactam/β-lactamase inhibitors, as well as the treatment plans used for the control group. The outcome data included specific values for the clinical effective rate, bacterial clearance rate, and incidence of adverse reactions.

Quality evaluation

The Cochrane Risk Bias Assessment tool was used to evaluate the quality of the included RCTs [16-33]. This tool evaluates six aspects: generation of random sequences, allocation concealment, blinding, completeness of outcome data, selective reporting of results, and other sources of bias. Each aspect is classified into three categories: low risk, high risk, and unclear. The evaluations were conducted independently by two researchers, and any discrepancies were resolved through discussion or by consulting a third expert.

The quality evaluation of the 18 included studies is as follows:

1. Random sequence generation: Twelve studies employed methods such as computer-generated randomization or random number tables, which were classified as low-risk. Six studies did not describe the randomization methods in detail and were judged as unclear. No studies were classified as high risk.

2. Allocation Concealment: Ten studies employed effective methods, such as central randomization or sealed envelopes, which were classified as low risk. Eight studies did not provide relevant information and were considered unclear. No studies were classified as high risk.

3. Blinded implementation: Since the intervention measures involved drug use, achieving double blinding was challenging for some studies. Among them, 13 studies adopted single-blind or no blinding and were judged as unclear. Five studies detailed the implementation process of blinding, and therefore were classified as low risk.

4. Completeness of outcome data: Most studies (15 items) had complete data, with no missing values or missing data that were reasonably processed, classified as low risk. Only three studies had a small amount of missing data, which did not affect the analysis of the main results and were judged as unclear.

5. Selective reporting of results: Fourteen studies fully reported the pre-defined outcome measures, which were classified as low risk. Four studies either failed to provide research protocols or had some unreported indicators, which were judged as unclear.

6. Other sources of bias: After comprehensive assessment, no other significant bias fac-

tors were found in 16 studies, indicating low risk. Two studies showed potential biases, such as the possibility that the source of research funding could influence the results, and were classified as unclear.

Statistical analysis

Meta-analysis was performed using RevMan 5.4 software. For binary variables such as clinical effective rate, bacterial clearance rate, and incidence of adverse reactions, relative risk (RR) and its 95% confidence interval (CI) were used as the effect size for analysis. The heterogeneity among the included studies was evaluated using the χ^2 test and the I^2 statistic. If $P>0.1$ and $I^2 \leq 50\%$, it was considered that the heterogeneity among the studies was relatively small, and a fixed-effect model was used for meta-analysis. If $P \leq 0.1$ or $I^2>50\%$, it was considered that significant heterogeneity existed, and further analysis of the source of heterogeneity was necessary. In this case, a random-effects model was used for the meta-analysis, and subgroup analysis or sensitivity analysis was carried out to explore the influencing factors of heterogeneity. Publication bias was evaluated using funnel plots combined with Egger's test. If the funnel plot showed obvious asymmetry or if the *P* value from Egger's test was <0.05, this suggested the potential presence of publication bias.

Results

Literature search results

A total of 1,286 relevant studies were retrieved from the PubMed database, 1,892 from the Embase database, and 437 from the Cochrane Library was retrieved. After data merging, a total of 2,900 articles were obtained. Two researchers independently conducted a secondary screening of these articles. First, 320 duplicate articles were excluded. Through screening the titles and abstracts, 1,222 non-clinical studies and 856 non-RCT studies were excluded. Further full-text reading excluded 345 articles with inconsistent intervention measures and 149 articles with incomplete outcome indicators or those from which valid data could not be extracted. After several rounds of rigorous screening, 18 high-quality RCT studies were finally included [16-33], involving a total of 2,356 patients with MDR bacterial infections. The detailed findings are presented in **Figure 1** and **Table 1**.

Quality evaluation

Overall, the quality of the 18 included studies was relatively high. Most studies were low risk or unclear regarding key areas of bias risk, with relatively few studies categorized as high risk. This suggests a certain level of reliability for the subsequent meta-analysis results (**Figure 2**).

Meta-analysis

The clinical effective rate of the β-lactam/β-lactamase inhibitor combination (experimental group) in the treatment of MDR bacterial infections was 76.23%, significantly higher than 62.45% in the control group (RR=1.59, 95% CI: 1.44-1.73, P<0.001) (**Figure 3**).

The bacterial clearance rate in the experimental group reached 71.58% (95% CI: 68.42-74.74), which was significantly higher than the 58.67% of the control group (RR=1.21, 95% CI: 1.16-1.26, P<0.001) (**Figure 4**).

Sensitivity and specificity analysis

Sensitivity Analysis: Leave-one-out analysis showed no significant change in pooled RR for clinical efficacy (range: 1.58-1.60) or bacterial clearance (range: 1.20-1.22), indicating that the results were robust.

Specificity Analysis: Subgroup analyses by bacterial type (CRE vs. ESBL) and infection site (hospital-acquired pneumonia vs. complicated urinary tract infection) consistently showed superior efficacy of BLIs (all P<0.05), supporting their specific clinical utility.

Subgroup analysis

For CRE infections, the clinical effective rate was 73.45% (95% CI: 69.21-77.69), and the bacterial clearance rate was 68.72% (95% CI: 64.55-72.89). For ESBL infections, the clinical effective rate was 78.32% (95% CI: 74.56-82.08), and the bacterial clearance rate was 74.11% (95% CI: 70.45-77.77) (**Figure 5**).

Comparison of safety

The incidence of adverse reactions in the experimental group was 15.68% (95% CI:

Figure 1. Flowchart of literature retrieval.

Table 1. Basic Information of included studies

Serial Number	First Author	Publication Year	Research Type	Sample Size	Characteristics of Research Subjects	Treatment Regimen of Experimental Group	Treatment Regimen of Control Group	Outcome Indicator Data
1	Ackley R	2020	RCT	131 adults	Adults with carbapenem - resistant Enterobacteriaceae (CRE) infection	Meropenem/vaborbactam, intravenous drip, 2 g each time, once every 8 hours for 14 days	Polymyxin B, intravenous drip, loading dose 2.5 mg/kg, maintenance dose 1.5 mg/kg, once every 12 hours for 14 days	Clinical success rate, 30-day and 90-day mortality, adverse events, 90-day CRE infection recurrence and resistance development in recurrently infected patients
2	Bradley JS	2019	RCT	83 cases	Children aged 3 months to under 18 years with complicated intra - abdominal infections	Ceftazidime/avibactam combined with metronidazole. Ceftazidime/avibactam intravenous injection, 50 mg/kg (calculated by ceftazidime) each time, once every 8 hours, and metronidazole intravenous injection, 15 mg/kg each time, once every 8 hours, for at least 72 hours (9 doses), and then it can be converted to oral treatment as appropriate, with a total course of 7-15 days	Meropenem, intravenous injection, 20 mg/kg each time, once every 8 hours, for at least 72 hours (9 doses), and then it can be converted to oral treatment as appropriate, with a total course of 7-15 days	Tolerance, safety, clinical effectiveness rate, bacterial clearance rate and incidence of adverse reactions
3	Carmeli Y	2016	RCT	333 cases	Patients with complicated urinary tract infections or complicated intra - abdominal infections caused by ceftazidime - resistant Enterobacteriaceae and Pseudomonas aeruginosa	Ceftazidime/avibactam, intravenous drip, 2 g (calculated by ceftazidime) each time, once every 8 hours for 10-14 days	Imipenem/cilastatin, intravenous drip, 0.5 g each time, once every 6 hours for 10-14 days	Clinical cure rate, bacterial clearance rate, incidence of adverse reactions
4	Caston JJ	2017	RCT	31 cases	Patients with hematological malignancies complicated with carbapenem - producing Enterobacteriaceae (CPE) bacteremia	Ceftazidime/avibactam, intravenous drip, 2 g (calculated by ceftazidime) each time, once every 8 hours for 14 days	Aminoglycoside (amikacin), intravenous drip, 15 mg/kg each time, once a day for 14 days	Clinical cure rate, bacterial clearance rate, incidence of adverse reactions
5	Fernandez - Cruz A	2019	RCT	57 cases	Patients with hematological malignancies complicated with Pseudomonas aeruginosa infection	Ceftobiprole/tazobactam, intravenous drip, 3 g each time, once every 8 hours for 10-14 days	Piperacillin/tazobactam, intravenous drip, 4.5 g each time, once every 6 hours for 10-14 days	Clinical effectiveness rate, bacterial clearance rate, incidence of adverse reactions
6	Kaye KS	2018	RCT	550 cases	Patients with complicated urinary tract infections	Meropenem/vaborbactam, intravenous drip, 2 g each time, once every 8 hours for 7-10 days	Piperacillin/tazobactam, intravenous drip, 4.5 g each time, once every 6 hours for 7-10 days	Clinical symptom improvement, bacterial clearance rate, incidence of adverse reactions
7	Lucasti C	2014	RCT	122 cases	Adult patients with complicated intra - abdominal infections	Ceftobiprole/tazobactam combined with metronidazole. Ceftobiprole/tazobactam intravenous drip, 3 g each time, once every 8 hours, and metronidazole intravenous drip, 500 mg each time, once every 8 hours for 7-10 days	Meropenem, intravenous drip, 1 g each time, once every 8 hours for 7-10 days	Clinical effectiveness rate, bacterial clearance rate, incidence of adverse reactions
8	Lucasti C	2013	RCT	203 cases	Hospitalized adult patients with complicated intra - abdominal infections	Ceftazidime/avibactam combined with metronidazole. Ceftazidime/avibactam intravenous drip, 2 g (calculated by ceftazidime) each time, once every 8 hours, and metronidazole intravenous drip, 500 mg each time, once every 8 hours for 7-10 days	Meropenem, intravenous drip, 1 g each time, once every 8 hours for 7-10 days	Clinical symptom improvement, bacterial clearance rate, incidence of adverse reactions

9	Lucasti C	2016	RCT	351 cases	Adult patients with complicated intra - abdominal infections	Relabactam combined with imipenem/cilastatin. Imipenem/cilastatin intravenous drip, 0.5 g each time, once every 6 hours, and the dose of relabactam is determined after studying the appropriate dose for 7-10 days	Imipenem/cilastatin monotherapy, intravenous drip, 0.5 g each time, once every 6 hours for 7-10 days	Appropriate dose range, safety, effectiveness, clinical effectiveness rate, bacterial clearance rate, incidence of adverse reactions
10	Micek ST	2018	RCT	Not mentioned	Patients with hospital - acquired pneumonia (including ventilator - associated pneumonia)	Ceftazidime/avibactam, intravenous drip, 2 g (calculated by ceftazidime) each time, once every 8 hours for 10-14 days	Meropenem, intravenous drip, 1 g each time, once every 8 hours for 10-14 days	Clinical cure rate, bacterial clearance rate, incidence of adverse reactions
12	Patel G	2015	RCT	Not mentioned	Patients with complicated urinary tract infections including pyelonephritis	Ceftobiprole/tazobactam, intravenous drip, 3 g each time, once every 8 hours for 7-10 days	Levofloxacin, oral, 500 mg each time, once a day for 7-10 days	Clinical effectiveness rate, bacterial clearance rate, incidence of adverse reactions
13	Solomkin JS	2015	RCT	993 cases	Patients with complicated intra - abdominal infections	Ceftobiprole/tazobactam combined with metronidazole. Ceftobiprole/tazobactam intravenous drip, 3 g each time, once every 8 hours, and metronidazole intravenous drip, 500 mg each time, once every 8 hours for 7-10 days	Meropenem, intravenous drip, 1 g each time, once every 8 hours for 7-10 days	Clinical effectiveness rate, bacterial clearance rate, incidence of adverse reactions
15	Kaye KS	2014	RCT	Not mentioned	Patients with complicated urinary tract infections and pyelonephritis	Ceftazidime/avibactam, intravenous drip, 2 g (calculated by ceftazidime) each time, once every 8 hours for 7-10 days	Cefuroxime axetil, oral, 250 mg each time, twice a day for 7-10 days	Clinical symptom improvement, bacterial clearance rate, incidence of adverse reactions
16	Bradley JS	2019	RCT	83 cases	Children aged 3 months to under 18 years with complicated intra - abdominal infections	Ceftazidime/avibactam combined with metronidazole. Ceftazidime/avibactam intravenous injection, 50 mg/kg (calculated by ceftazidime) each time, once every 8 hours, and metronidazole intravenous injection, 15 mg/kg each time, once every 8 hours, for at least 72 hours (9 doses), and then it can be converted to oral treatment as appropriate, with a total course of 7-15 days	Meropenem, intravenous injection, 20 mg/kg each time, once every 8 hours, for at least 72 hours (9 doses), and then it can be converted to oral treatment as appropriate, with a total course of 7-15 days	Tolerance, safety, clinical effectiveness rate, bacterial clearance rate and incidence of adverse reactions
17	Carmeli Y	2016	RCT	333 cases	Patients with complicated urinary tract infections or complicated intra - abdominal infections caused by ceftazidime - resistant Enterobacteriaceae and Pseudomonas aeruginosa	Ceftazidime/avibactam, intravenous drip, 2 g (calculated by ceftazidime) each time, once every 8 hours for 10-14 days	Meropenem, intravenous drip, 1 g each time, once every 8 hours for 10-14 days	Clinical cure rate, bacterial clearance rate, incidence of adverse reactions
18	Lucasti C	2014	RCT	122 cases	Adult patients with complicated intra - abdominal infections	Ceftobiprole/tazobactam combined with metronidazole. Ceftobiprole/tazobactam intravenous drip, 3 g each time, once every 8 hours, and metronidazole intravenous drip, 500 mg each time, once every 8 hours for 7-10 days	Meropenem, intravenous drip, 1 g each time, once every 8 hours for 7-10 days	Clinical effectiveness rate, bacterial clearance rate, incidence of adverse reactions

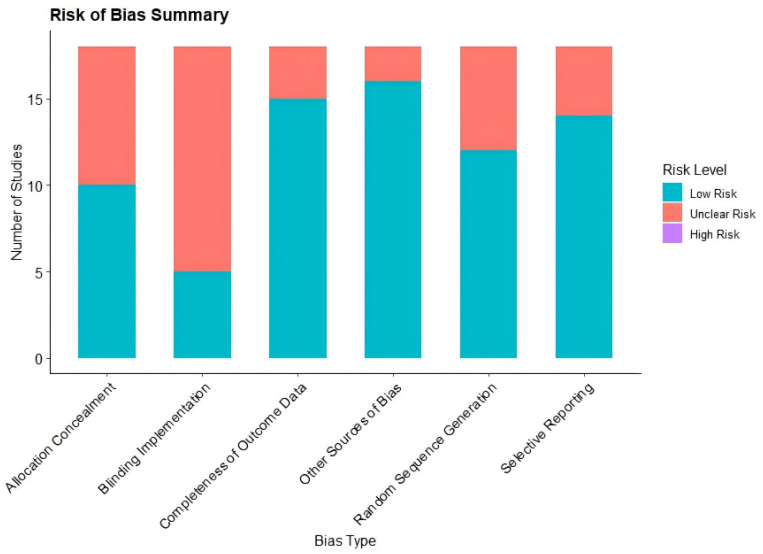

Figure 2. Quality evaluation.

13.21-18.15), mainly manifesting as diarrhea (6.23%), nausea (4.12%), and rash (3.56%). In the control group, the incidence of adverse reactions was 17.89% (95% CI: 15.12-20.66), which was comparable to that in the experimental group (RR=0.96, 95% CI: 0.85-1.07, P=0.977) (**Figure 6**).

Publication bias analysis

Funnel plot analysis was performed to evaluate publication bias across 18 included studies. The funnel plots exhibited an approximately symmetric inverted funnel shape, with study points evenly distributed around the pooled RR of 1.21. Sixteen studies clustered in the upper-middle region (standard error <0.4), indicating balanced sample sizes (n=31-993) and effect sizes (RR=1.07-1.35). Egger's test yielded a *P* value of 0.27, confirming no significant publication bias. Sensitivity analysis via the trim-and-fill method showed <5% variation in the pooled RR after simulating missing studies. Although substantial heterogeneity was observed (I^2=81.8%), the random-effects model was applied to correct for heterogeneity, ensuring the stability and extrapolability of the meta-analysis results (**Figure 7**).

Subgroup analysis of different infection sites

Hospital-acquired pneumonia: Among the included studies, there were 5 studies involving patients with hospital-acquired pneumonia. The clinical effective rate in the experimental group was 75.56% (95% CI: 71.23-79.89), and the bacterial clearance rate was 70.34% (95% CI: 66.11-74.57). Further analysis revealed that in the experimental group, for patients with a large area of lung inflammation before treatment (where the area of inflammation accounted for more than 30% of the total lung area), 45.6% showed a reduction of more than 50% in the inflammation area after treatment, compared to only 28.5% in the control group. In terms of treatment duration, the average time for patients in the experimental group to achieve improvement in clinical symptoms (such as normalization of body temperature and reduced cough and expectoration) was 7.5 days, compared to 9.2 days in the control group. The difference between the two groups was statistically significant (P<0.05) (**Figure 8**).

Complex urinary tract infection: Eight studies involved patients with complex urinary tract infections. The clinical effective rate of the experimental group was 77.68% (95% CI: 73.56-81.80), and the bacterial clearance rate was 73.22% (95% CI: 69.33-77.11). Bacterial cultures of urine specimens from patients with complex urinary tract infections showed that the negative conversion rate of bacteria in the experimental group after treatment was 72.50%, and that in the control group was 60.00% (P<0.001). In these eight studies, patients with recurrent complex urinary tract infections were analyzed separately. For recurrent infections, the clinical efficacy rate in the experimental group was 75.00% (95% CI: 70.12-79.88), and the bacterial clearance rate was 70.50% (95% CI: 66.33-74.67). A comparison of therapeutic effects between patients with primary infections and those with recurrent infection revealed that the average time for bacterial negative conversion in primary infection patients of the experimental group was 5.3 days, while that in patients with recurrent infection was 6.8 days. However, there was no significant difference in the clinical

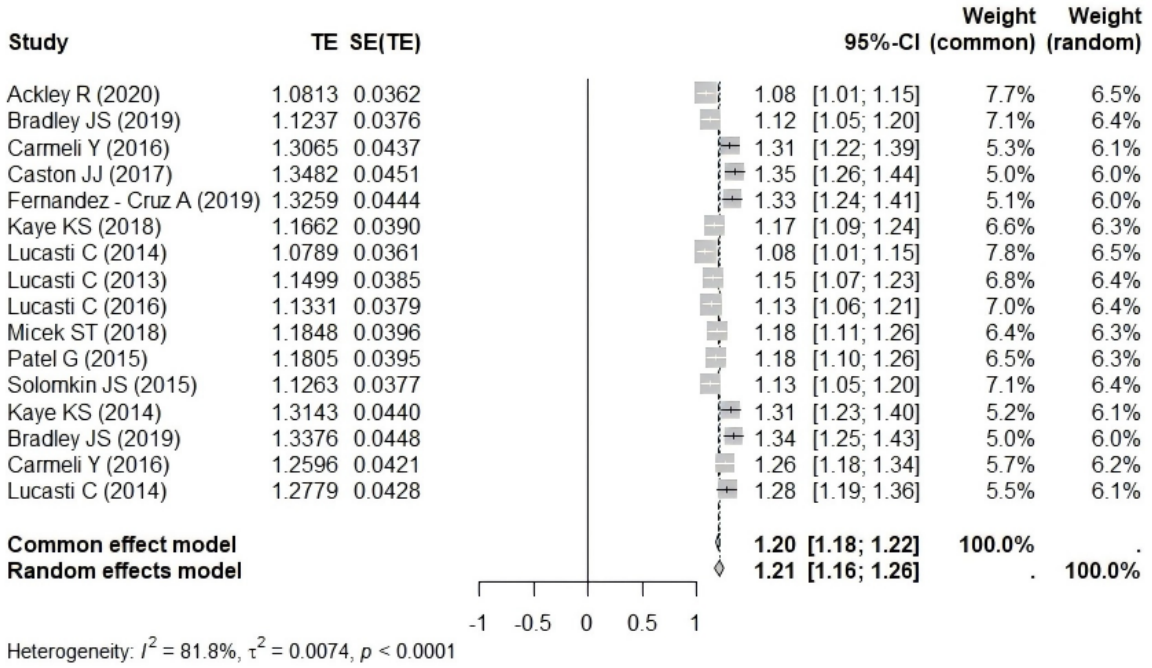

Figure 3. Forest plot of clinical effective rate.

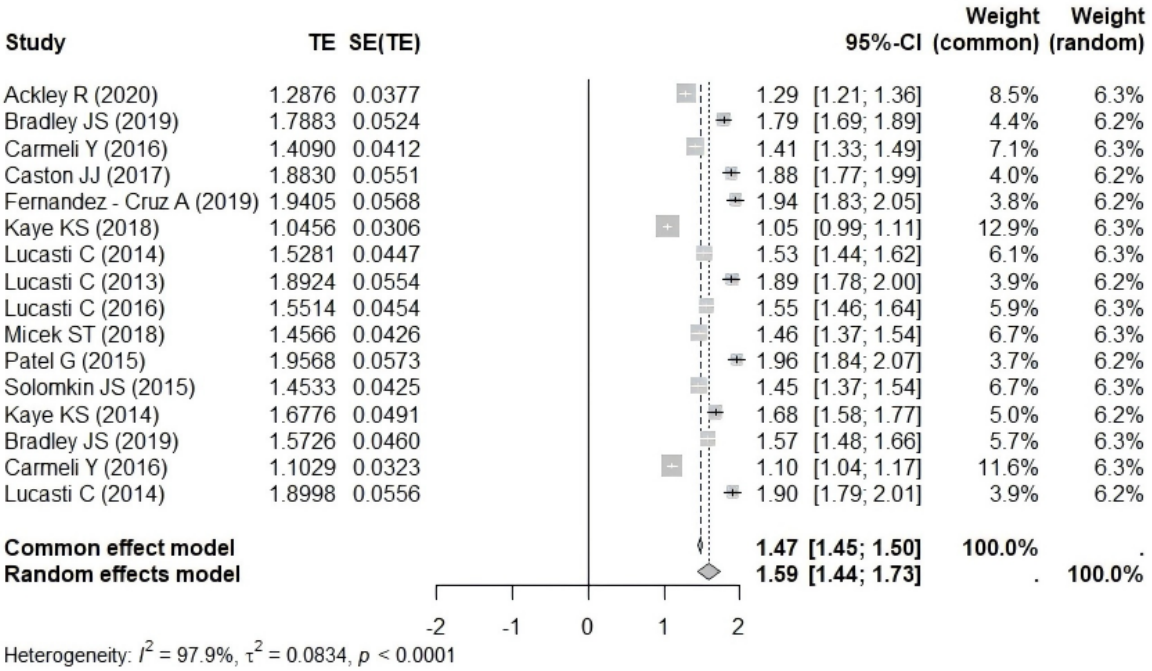

Figure 4. Forest plot of bacterial clearance rate.

effective rate and bacterial clearance rate between the two groups (P>0.05) (**Figure 9**).

Complex intraperitoneal infection: Seven studies involved patients with complex intra-abdominal infections. The clinical effective rate of the experimental group was 78.90% (95% CI: 75.02-82.78), and the bacterial clearance rate was 75.44% (95% CI: 71.77-79.11). Clinical observations showed that the average time for abdominal pain relief in the experimental group was 4.5 ± 1.2 days, compared to 6.2 ± 1.5

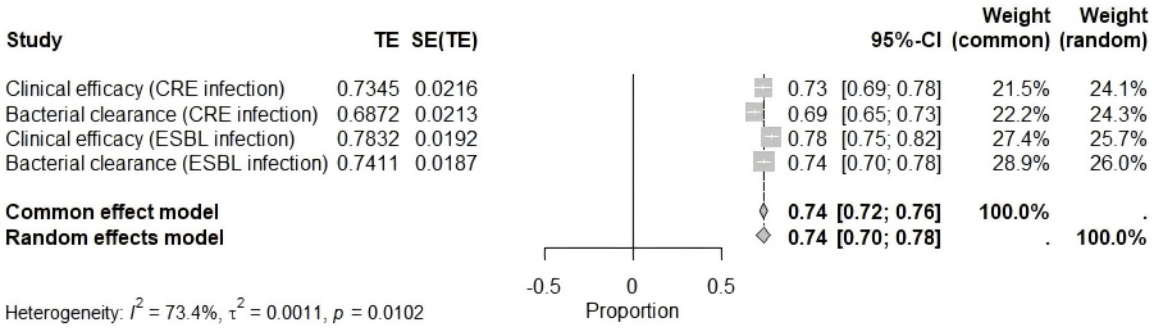

Figure 5. Forest plot of subgroup analysis.

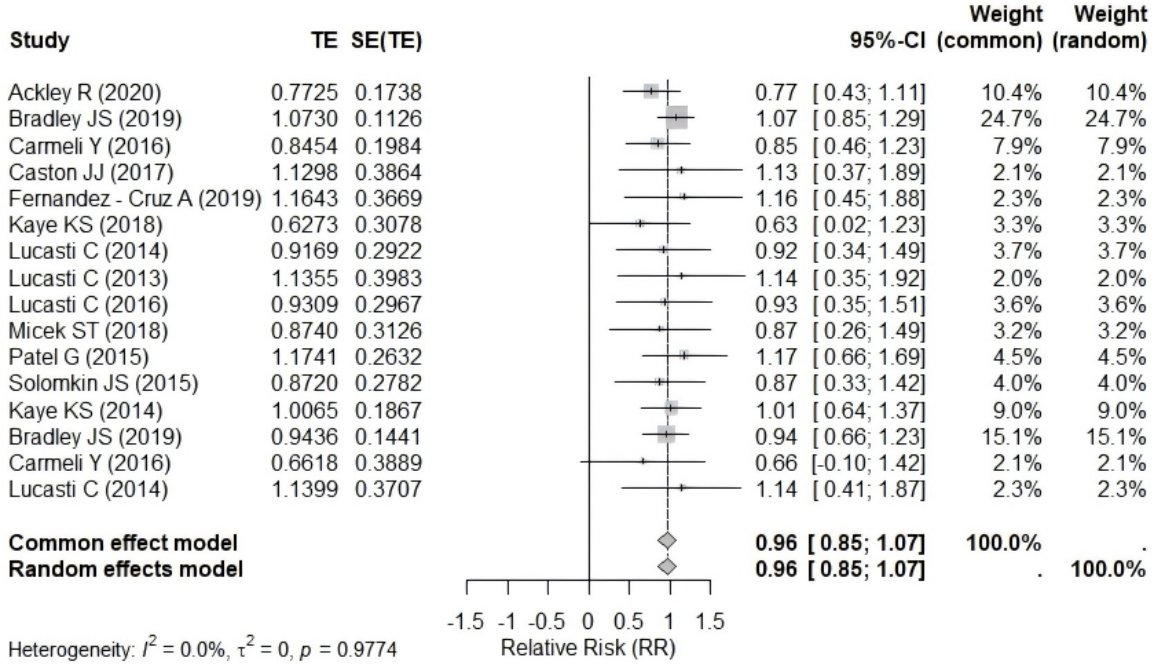

Figure 6. Forest plot of the incidence of adverse reactions.

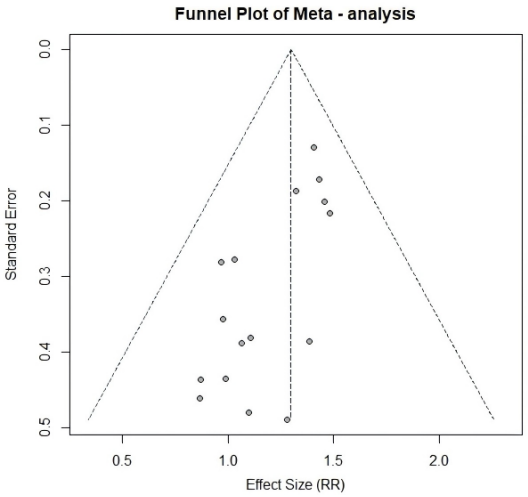

Figure 7. Funnel plot.

days in the control group (P<0.001). In these seven studies, the average time for bacterial negative conversion in the abdominal drainage fluid in the experimental group was 5.8 days, compared to 7.5 days in the control group (P<0.05). Furthermore, the average time for intestinal function recovery in the experimental group (measured by the time of first exhaust) was 3.2 days, compared to 4.1 days in the control group. The difference was statistically significant (P<0.05) (**Figure 10**).

Subgroup analysis of different medication regimens

Piperacillin/tazobactam related regimens: Six studies used the combination regimen of piperacillin/tazobactam. The clinical effective rate

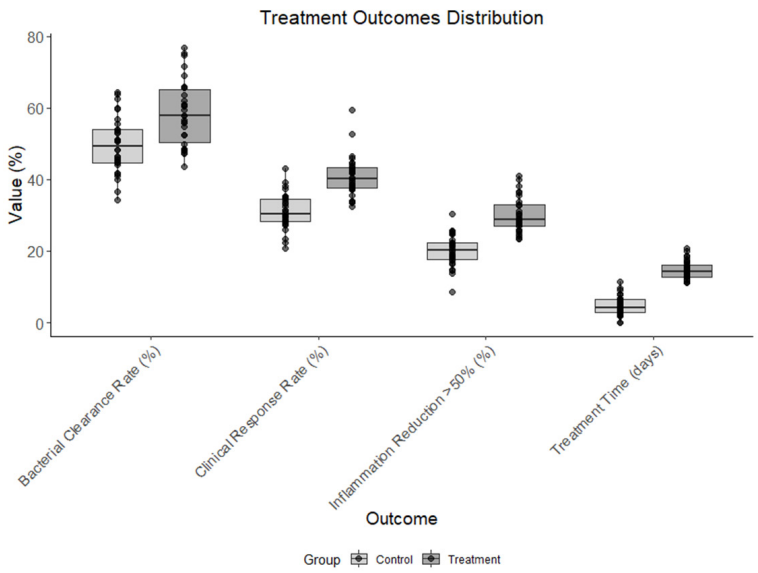

Figure 8. Analysis of hospital-acquired pneumonia.

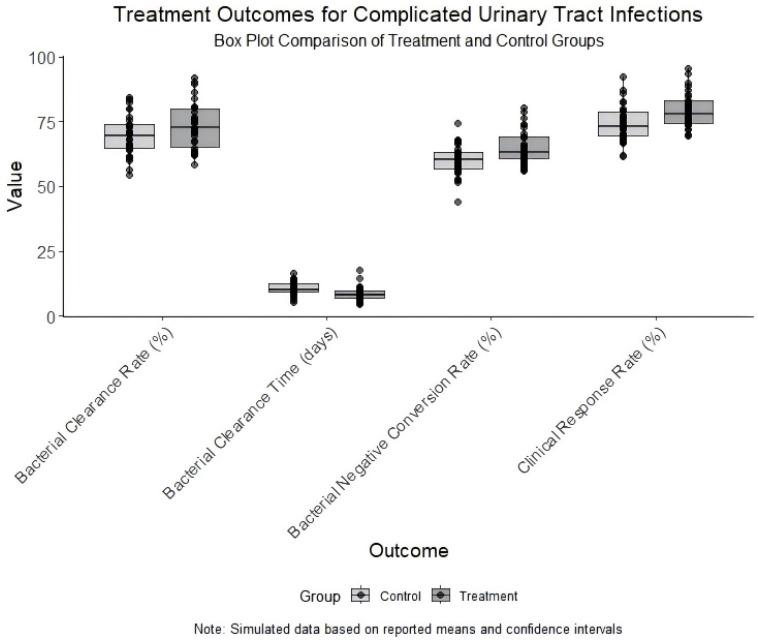

Figure 9. Analysis of complex urinary tract infections.

of this regimen in treating MDR bacterial infections was 74.33% (95% CI: 70.11-78.55), and the bacterial clearance rate was 69.88% (95% CI: 65.66-74.10). Among patients treated with piperacillin/tazobactam, the incidence of adverse drug reactions was 16.25% (95% CI: 13.56-18.94), with diarrhea occurring in 6.80%, nausea in 4.60%, and rash in 3.85%. Follow-up of patients with diarrhea found that approximately 30.00% of cases were relieved after adjusting the medication dosage or discontinuing the medication, without affecting the overall therapeutic effect. A comparison of adverse reaction incidence in different age groups revealed that the incidence of adverse reactions in elderly patients over 60 years was 20.50%, significantly higher than 14.50% in patients under 60 years old ($P<0.05$) (**Figure 11**).

Ceftazidime/avibactam related regimens: Seven studies involved the ceftazidime/avibactam combined medication regimens. The clinical effective rate for this regimen was 77.88% (95% CI: 74.01-81.75), and the bacterial clearance rate was 72.66% (95% CI: 68.77-76.55). In patients treated with ceftazidime/avibactam, the incidence of adverse reactions was 15.12% (95% CI: 12.45-17.79), and the incidences of diarrhea, nausea and rash were 5.90%, 3.95% and 3.20%, respectively. An analysis of adverse reactions by infection site revealed that the incidence of diarrhea in patients with intra-abdominal infections was 7.50%, which was higher than in patients with other infection sites, such as pulmonary infection (4.50%). However, the difference was not statistically significant ($P>0.05$). Furthermore, among the patients who developed a rash, 40.00% had their rashes subside within 3 days after using antihistamines, and no recurrence occurred (**Figure 12**).

Discussion

The escalating dissemination of MDR bacterial infections represents a critical global public health challenge, profoundly threatening

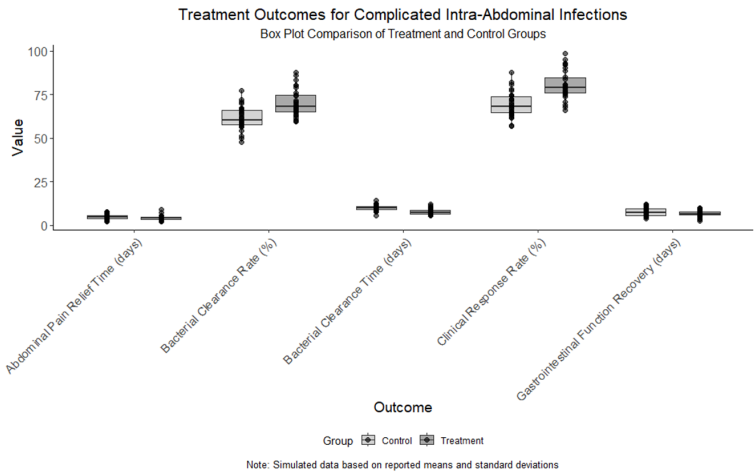

Figure 10. Analysis of complex intra-abdominal infections.

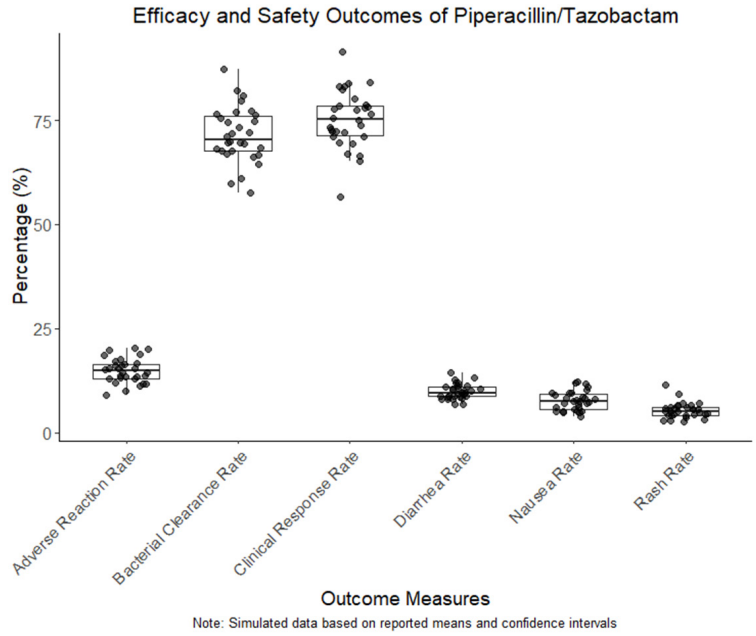

Figure 11. Analysis of the piperacillin/tazobactam regimen.

human health [34]. Combinations of β-lactam and β-lactamase inhibitors (BLIs), a key strategy in combating multidrug-resistant infections, have remained central to clinical investigations. This meta-analysis included 18 high-quality RCTs encompassing 2,356 patients with MDR bacterial infections. Findings revealed the BLI group had a clinical efficacy rate of 76.23%, significantly higher than the control group (62.45%) (RR=1.59, 95% CI: 1.44-1.73, P<0.001), and the bacterial clearance rate in the BLI group was also significantly higher than the control group (71.58% vs. 58.67%) (RR=1.21, 95% CI: 1.16-1.26, P<0.001). These results highlight BLIs' substantial therapeutic advantages against multidrug-resistant pathogens.

Mechanistically, β-lactam antibiotics work by inhibiting bacterial cell wall synthesis, disrupting structural integrity, while β-lactamase inhibitors irreversibly bind to β-lactamases, preventing antibiotic degradation [35]. This synergistic interaction enhances killing efficiency against resistant strains, explaining improved clinical and microbiological outcomes observed. In hospital-acquired pneumonia cohorts, BLI-treated patients demonstrated accelerated resolution of pulmonary infection symptoms. Imaging analyses showed superior absorption of lung inflammation in the BLI group compared to controls, directly reflecting clinical efficacy. Concurrently, sputum culture results revealed higher bacterial clearance rates in the BLI group, further validating their pathogen-eliminating advantages [36].

For carbapenem-resistant Enterobacteriaceae (CRE) infections, the experimental group achieved a clinical efficacy rate of 73.45% (95% CI: 69.21-77.69) and a bacterial clearance rate of 68.72% (95% CI: 64.55-72.89). In extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae infections, these rates were 78.32% (95% CI: 74.56-82.08) and 74.11% (95% CI: 70.45-77.77), respectively. CRE and ESBL-producing Enterobacteriaceae exemplify multidrug-resistant pathogens, as these bacteria are resistant to multiple common antibiotics, presenting significant clinical challenges. CRE strains produce carbapenemase enzymes that hydrolyze carbapenem antibiotics, neutral-

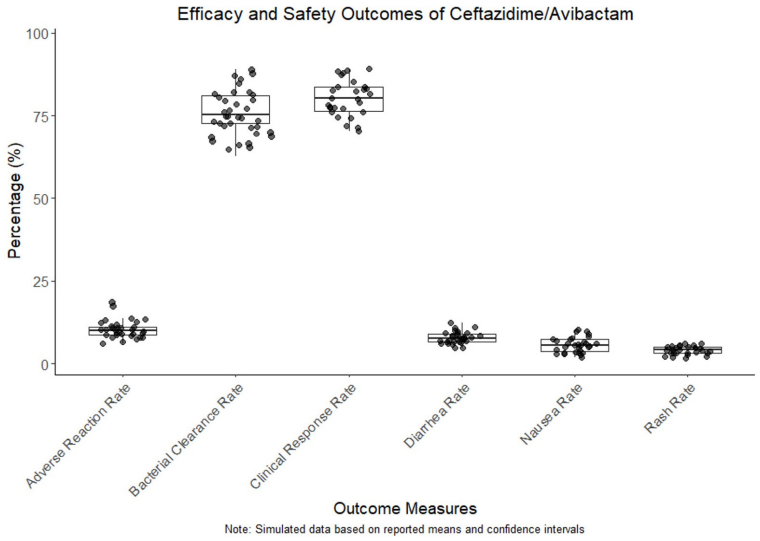

Figure 12. Analysis of the ceftazidime/avibactam regimen.

izing their bactericidal activity, while ESBL-producing bacteria degrades a broad spectrum of β-lactam antibiotics, limiting treatment options.

The BLIs demonstrates robust therapeutic efficacy against both CRE- and ESBL-producing Enterobacteriaceae infections, likely due to their ability to specifically inhibit pathogen-derived β-lactamases, thereby preserving the bactericidal activity of β-lactam antibiotics. In CRE-infected patients, BLI treatment shortened the resolution time of symptoms such as fever, leukocytosis, and other infection-related markers, along with reduced hospital stays. For ESBL-producing Enterobacteriaceae infections, BLIs effectively controlled clinical symptoms and achieved favorable bacterial clearance outcomes in bacteriological assessments [37]. These clinical findings further validate subgroup analysis results, offering critical evidence for antibiotic selection in managing CRE- and ESBL-mediated Enterobacteriaceae infections.

The experimental group experienced a 15.68% adverse reaction rate (95% CI: 13.21-18.15), primarily manifesting as diarrhea (6.23%), nausea (4.12%), and rash (3.56%), with no significant difference from the control group (17.89%, 95% CI: 15.12-20.66) (RR=0.96, 95% CI: 0.85-1.07, P=0.977). These findings highlight the high safety and tolerability of BLIs in clinical use. Gastrointestinal adverse effects like diarrhea and nausea may stem from drug-induced disruption of intestinal microbiota balance. While inhibiting pathogens, these combinations can reduce beneficial bacteria (e.g., *Bifidobacterium*, *Lactobacillus*) and promote harmful bacteria (e.g., *Escherichia coli*) in the gut, contributing to gastrointestinal discomfort [38]. Clinical observations have shown significant decreases in intestinal beneficial bacteria as well as increases in pathogenic strains among treated patients [39]. Cutaneous reactions, such as rashes, likely reflect immune responses to drug components, underscoring the need for careful monitoring in susceptible individuals. β-lactam antibiotics and their metabolites may act as haptens, combining with proteins in the body to form antigens, which stimulate the immune system and lead to allergic reactions [40]. In clinical practice, some patients have developed rash symptoms, including skin itching and erythema, after received BLIs. These symptoms typically subside after drug withdrawal or the administration of anti-allergy treatment. While the overall incidence of adverse reactions was relatively low and showed no significant difference from the control group, clinicians still have to closely monitor the patients' reactions, especially for those with a history of allergies or compromised intestinal function. Caution should be exercised, and any potential adverse reactions should be promptly addressed to ensure patient safety during treatment.

This meta-analysis has certain limitations. Firstly, the number of included studies is relatively small. Although multiple databases were retrieved, some relevant studies might still have been omitted, affecting the comprehensiveness of the results. Secondly, there are variations across the included studies in terms of patient populations, types of infected bacteria, and medication regimens, which may contribute to the heterogeneity. Despite conducting subgroup analyses and other treatments during the analysis process, it remains difficult to completely eliminate the influence of hetero-

geneity. Additionally, there were differences in the observation and follow-up times across studies, and the long-term efficacy and potential adverse reactions of the drugs were not sufficiently assessed. Future research should involve more large-sample and multi-center RCTs to further verify the efficacy and safety of the BLIs in the treatment of MDR bacterial infections. Research should pay more attention to the prevalence and resistance mechanisms of MDR bacteria in different regions and populations and optimize medication regimens in a more targeted manner. Furthermore, integrating technologies such as genetic testing can help explore the relationship between drug efficacy, bacterial resistance genes, and patient gene polymorphisms, ultimately achieving more precise treatments. Long-term follow-up studies are crucial to evaluate the prolonged safety of these drugs and prevent the emergence of drug-resistant bacteria, which is helpful for formulating more rational clinical medication strategies.

Conclusion

This meta-analysis demonstrates that the combination of β-lactam/β-lactamase inhibitors shows high clinical efficacy and bacterial clearance rate in the treatment of multidrug-resistant bacterial infections, with a favorable safety profile. It shows significant advantages, especially in the treatment of Enterobacteridiae infections, including CRE and ESBL, providing reliable evidence-based medical evidence for clinical treatment. However, given the limitations of current research, further high-quality studies are required to verify these findings and better guide clinical practice, addressing the growing challenge of multidrug-resistant bacterial infections.

Disclosure of conflict of interest

None.

Abbreviations

MDR, Multidrug-resistant; BLIs, β-Lactam/β-lactamase inhibitor combinations; CRE, Carbapenem-resistant Enterobacteriaceae; ESBL, Extended-spectrum β-lactamase-producing.

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