INPLASY

Efficacy and Safety of Novel β-Lactam/β-Lactamase Inhibitor Combinations for the Treatment of Complicated Urinary Tract Infections or Acute Pyelonephritis: A Systematic review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 September 2025 and was last updated on 14 September 2025.

INTRODUCTION

Review question / Objective Review question: In patients with complicated urinary tract infections (cUTI) or acute pyelonephritis (APN), do novel β-lactam/β-lactamase inhibitor (BL/BLI) combinations improve clinical and microbiological outcomes compared with standard-of-care antibiotics or placebo?
Objectives:
Using evidence from randomized controlled trials, this systematic review and meta-analysis aims to:
(1) Assess the efficacy of novel BL/BLI combinations (e.g., ceftazidime–avibactam, ceftolozane–tazobactam, meropenem–vaborbactam, imipenem–relebactam, cefepime–enmetazobactam, cefepime–taniborbactam) in the treatment of cUTI and APN.
(2) Evaluate microbiological eradication rates and safety outcomes (drug-related adverse events, serious adverse events, treatment discontinuations, and mortality).
(3) Explore sources of heterogeneity using subgroup and meta-regression analyses.

Rationale Complicated urinary tract infections (cUTI) and acute pyelonephritis (APN) represent a major global health burden, particularly due to the rising prevalence of multidrug-resistant Gram-negative bacteria. Traditional agents such as carbapenems and fluoroquinolones are increasingly compromised by extended-spectrum

β-lactamases (ESBLs), AmpC enzymes, and carbapenemases, limiting effective treatment options. Novel β-lactam/β-lactamase inhibitor (BL/BLI) combinations have been developed to address these resistance mechanisms.

Although several randomized controlled trials (RCTs) have evaluated the efficacy and safety of these novel agents, the evidence remains fragmented across different drug regimens, patient populations, and geographic regions. Prior reviews have often focused on single agents or specific subgroups rather than providing a comprehensive synthesis.

This systematic review and meta-analysis is therefore needed to pool and critically appraise the available RCT evidence, offering a robust evaluation of efficacy, microbiological eradication, and safety outcomes. The findings will support clinical decision-making, guide antimicrobial stewardship, and identify gaps for future research, particularly regarding metallo-β-lactamase producers.

Condition being studied Complicated urinary tract infections (cUTI) and acute pyelonephritis (APN) are serious infections of the urinary tract that extend beyond uncomplicated cystitis, often associated with structural or functional abnormalities of the urinary tract. These conditions are commonly caused by Gram-negative bacteria such as Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Enterobacter cloacae. They are frequently linked to multidrug resistance, including extended-spectrum β-lactamase (ESBL) and carbapenemase production, which significantly limits therapeutic options. Effective management of cUTI and APN is therefore a critical concern in clinical practice.

METHODS

Search strategy PubMed Search Strategy: ("Urinary Tract Infections"[Mesh] OR "cUTI" OR "complicated urinary tract infection" OR "acute pyelonephritis") AND ("Ceftazidime-avibactam" OR "Ceftolozane-tazobactam" OR "Meropenem-vaborbactam" OR "Imipenem-relebactam" OR "Cefepime-enmetazobactam" OR "Cefepime-taniborbactam")

Embase Search Strategy: 'complicated urinary tract infection'/exp OR 'acute pyelonephritis'/exp OR cUTI OR APN AND ('ceftazidime avibactam'/exp OR 'ceftolozane tazobactam'/exp OR 'meropenem vaborbactam'/exp OR 'imipenem relebactam'/exp OR 'cefepime enmetazobactam'/exp OR 'cefepime taniborbactam'/exp)

Cochrane Library Search Strategy: ("complicated urinary tract infection" OR "cUTI" OR "acute pyelonephritis") AND ("ceftazidime-avibactam" OR "ceftolozane-tazobactam" OR "meropenem-vaborbactam" OR "imipenem-relebactam" OR "cefepime-enmetazobactam" OR "cefepime-taniborbactam")

Web of Science Search Strategy: TS=("complicated urinary tract infection" OR "acute pyelonephritis") AND TS=("ceftazidime-avibactam" OR "ceftolozane-tazobactam" OR "meropenem-vaborbactam" OR "imipenem-relebactam" OR "cefepime-enmetazobactam" OR "cefepime-taniborbactam")

ClinicalTrails.gov Search Strategy: Condition or disease: "urinary tract infection" OR "pyelonephritis"

Other terms: "ceftazidime-avibactam", "ceftolozane-tazobactam", "meropenem-vaborbactam", "imipenem-relebactam", "cefepime-enmetazobactam", "cefepime-taniborbactam"

FDA.gov Search Strategy: Keyword search: "ceftazidime-avibactam", "ceftolozane-tazobactam", "meropenem-vaborbactam", "imipenem-relebactam", "cefepime-enmetazobactam", "cefepime-taniborbactam" within Drug Approval or Labeling databases.

Participant or population This review will include patients diagnosed with complicated urinary tract infections (cUTI) or acute pyelonephritis (APN), as defined by the original randomized controlled trials. Both adult and pediatric populations will be eligible, regardless of sex. Patients with infections caused by Gram-negative bacteria such as Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter cloacae, and Citrobacter spp. will be included.

Exclusion criteria are studies limited to uncomplicated urinary tract infections, prophylactic antibiotic use, or non-bacterial etiologies.

Intervention The interventions of interest are novel β-lactam/β-lactamase inhibitor (BL/BLI) combinations used for the treatment of complicated urinary tract infections (cUTI) or acute pyelonephritis (APN). These include: Ceftazidime–avibactam, Ceftolozane–tazobactam, Meropenem–vaborbactam, Imipenem–relebactam, Cefepime–enmetazobactam, Cefepime–taniborbactam.

Comparator The comparators will include standard-of-care antibiotics or placebo, as reported in the included randomized controlled trials. Specifically, comparators may consist of: Carbapenems (e.g., meropenem, imipenem), Cephalosporins (e.g., cefepime, ceftazidime),

Fluoroquinolones (e.g., levofloxacin, ciprofloxacin), Placebo (if applicable).

Study designs to be included Only randomized controlled trials (RCTs) will be included in this review, as they provide the highest level of evidence for evaluating the efficacy and safety of novel β-lactam/β-lactamase inhibitor (BL/BLI) combinations.Exclusion criteria: observational studies, cohort studies, case–control studies, case series, case reports, reviews, and conference abstracts without full-text publication.

Eligibility criteria We included RCTs that enrolled patients with a diagnosis of cUTI or APN based on clinical criteria (e.g., fever, flank pain, systemic symptoms, or radiographic evidence of renal involvement) and/or microbiological confirmation (baseline uropathogen ≥105 CFU/mL). Eligible participants were adults (≥18 years) as well as pediatric patients when outcome data were reported separately. Interventions of interest were novel β-Lactam/β-Lactamase inhibitor combinations—such as ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam, cefepime-enmetazobactam, or cefepime-taniborbactam—administered at standard therapeutic doses. Comparators included conventional antibiotics commonly used in clinical practice (e.g., carbapenems, cephalosporins, fluoroquinolones, or piperacillin-tazobactam). Studies were required to report at least one predefined primary or secondary outcome, including clinical cure, microbiological eradication,adverse events (AEs), serious AEs (SAEs), drug-related AEs (DRAEs), AEs leading to treatment discontinuation (AEsLDT).
We excluded non-randomized studies (e.g., observational cohorts, case series, case-control studies), in vitro or animal experiments, and pharmacokinetic/pharmacodynamic investigations. Reviews, editorials, and conference abstracts without extractable outcome data were also excluded. Studies focusing primarily on non-urinary infections were excluded unless cUTI/APN-specific outcomes were reported separately. Trials with inappropriate dosing regimens, duplicated publications, or insufficient data on efficacy or safety endpoints were not considered.

Information sources
The following information sources will be used:
Electronic databases: PubMed, Embase, Web of Science, and Cochrane Library will be searched .
Trial registers: ClinicalTrials.gov will be screened to identify unpublished or ongoing randomized controlled trials.
Other sources: Reference lists of included studies will be checked (backward citation searching), and forward citation tracking will be performed using Web of Science.
Author contact: Study authors may be contacted if essential outcome data are missing or unclear.
No language restrictions will be applied.

Main outcome(s) The primary outcome of this review will be clinical efficacy, defined as clinical cure or improvement at the test-of-cure (TOC) visit or at the end-of-therapy (EOT), according to the definitions used in the included randomized controlled trials.
Effect measures: outcomes will be analyzed as odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous data.

Additional outcome(s) Microbiological eradication at test-of-cure (TOC) or end-of-therapy (EOT), as defined in the included trials.
Modified microbiological intent-to-treat (m-mITT) response, reflecting pathogen-specific eradication rates.
Drug-related adverse events (DRAEs), including incidence and type of adverse reactions.
Serious adverse events (SAEs) and treatment discontinuations due to adverse events.
All-cause mortality during treatment or follow-up period, if reported.
Effect measures: dichotomous outcomes will be expressed as odds ratios (ORs) with 95% CIs.

Data management All references identified through electronic database searches will be imported into EndNote X9 (Clarivate Analytics) for citation management, and duplicates will be removed. Screening of titles, abstracts, and full texts will be performed independently by two reviewers.
Data from eligible studies will be extracted into a pre-designed Microsoft Excel form that captures study characteristics, interventions, comparators, outcomes, and risk of bias assessments. Extracted data will be cross-checked by a second reviewer to ensure accuracy.
The final dataset will be stored securely with version control, and discrepancies will be resolved by discussion or consultation with a third reviewer.

Quality assessment / Risk of bias analysis The risk of bias in the included RCTs was assessed independently by two reviewers using the Cochran Risk of Bias 2.0 (RoB 2) tool. This tool evaluates five domains of potential bias: (1) the randomization process; (2) deviations from intended interventions; (3) missing outcome data;

(4) measurement of the outcome; (5) selection of the report result.
Each domain was rated as 'low risk', 'moderate risk', or 'high risk', following the signaling questions and algorithm specified in the RoB 2.0 handbook. A study-level summary judgment was then derived based on the domain-level assessment. Discrepancies between the two reviewers were resolved through discussion and consensus, and a third reviewer was consulted when necessary.

Strategy of data synthesis For each outcome, we selected the statistical model (fixed-effects model [FEM] or random-effects model [REM]) based on the degree of heterogeneity, assessed by the I2 statistic and Cochran's Q test. For CE and ME, REMs were applied when $I2 > 50\%$ or $p < 0.10$ for Cochran's Q; otherwise, FEMs were used. This threshold for I^2 follows the conventional interpretation of heterogeneity proposed and adopted in the Cochrane Handbook [17, 18]. For safety outcomes, including AEs, SAEs, AEsLDT, and DRAEs, model selection followed the same principle. In addition to reporting pooled Odds Ratios (OR) and 95% Confidence Interval (CI), we calculated 95% prediction interval for REMs to estimate the expected range of true effects in future studies.
We also conducted a leave-one-out sensitivity analysis for key outcomes by iteratively omitting one study at a time to assess the influence of individual studies on the pooled results. Subgroup analyses were performed based on the type of β-Lactam/β-Lactamase inhibitor used.
To further explore potential sources of heterogeneity, we performed exploratory meta-regression analyses for the major efficacy endpoints, including CE at EOT, CE at TOC, ME at TOC, and m-mITT at TOC. The study-level covariates assessed were publication year (continuous), drug class (categorical: ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam, cefepime-enmetazobactam, cefepime-taniborbactam), population type (adult vs pediatric), and total sample size (continuous).
Univariable models were first fitted to examine the effect of each covariate independently. Multivariable models including year, population type, and drug class were then explored when data permitted. All analyses were conducted under a random-effects framework using weighted least squares, with inverse-variance weights derived from each study's log odds ratio and variance. Regression coefficients, standard errors, and p-values were reported, and the proportion of between-study variance explained (R^2 analog) was calculated.
Meta-regression analyses were implemented in Python (version 3.10) using the statsmodels package (version 0.14.2).
OR with 95% confidence intervals were chosen as the summary effect measure for dichotomous outcomes rather than risk ratios (RR). OR were used because not all included trials reported consistent risk denominators, and outcome definitions (e.g., CE, c-mITT, m-mITT, ME) varied across studies. In such cases, OR provide a more statistically robust estimate and allow pooling of data from diverse trial designs. Moreover, OR are commonly recommended in meta-analyses of randomized controlled trials with binary endpoints, particularly when event rates differ across populations [18, 19].

Subgroup analysis Subgroup analyses will be performed when sufficient data are available. Planned subgroup comparisons include:
Population type: adults vs pediatric patients.
Drug regimen: individual BL/BLI combinations (e.g., ceftazidime–avibactam, ceftolozane–tazobactam, meropenem–vaborbactam, imipenem–relebactam, cefepime–enmetazobactam, cefepime–taniborbactam).
Follow-up time: short-term (test-of-cure) vs longer-term (end of therapy or post-treatment follow-up).
These analyses aim to explore potential sources of heterogeneity and differences in efficacy or safety across subgroups.

Sensitivity analysis Sensitivity analyses will be conducted to test the robustness of the pooled results. Planned methods include:
Comparing results using a fixed-effect model versus a random-effects model.
Leave-one-out analysis by sequentially removing individual studies to assess their influence on the overall effect estimate.
Excluding studies assessed as having a high risk of bias to evaluate the impact of study quality.
Restricting analyses to large trials (e.g., sample size >100 per arm) to minimize small-study effects.
These approaches will help determine whether the overall conclusions are driven by specific studies or analytical choices.

Language restriction No language restrictions will be applied during the literature search. Studies published in any language will be considered.

Country(ies) involved China.

Other relevant information This review follows the PRISMA 2020 reporting guidelines. A

completed PRISMA checklist and the full electronic search strategy are provided as supplementary materials. Although the review could not be prospectively registered in PROSPERO due to its advanced stage at the time of registration, the protocol has been documented and made available as supplementary material to ensure transparency.

Keywords Meta-analysis, Efficacy, Safety, Infection, β-Lactam/β-Lactamase inhibitor combinations.

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