



Efficacy of treatment options for complicated urinary tract infections including acute pyelonephritis: a systematic literature review and network meta-analysis

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Aim: Compared with uncomplicated urinary tract infections (UTIs), complicated UTIs (cUTIs) including acute pyelonephritis (AP) present with significant morbidity, a higher risk of treatment failure and typically require longer courses of treatment, or alternative antibiotics. The emergence of drug-resistant organisms represents a considerable challenge in the treatment of patients with cUTIs/AP and has limited antibiotic options. Carbapenems are considered the current last line of therapy, however, carbapenem resistance represents a growing problem. Although several established and novel treatment options are available, direct comparative evidence is lacking.

Methods: Randomized controlled trials (RCTs) were identified by systematic literature review of Embase®, MEDLINE® and Cochrane databases (database inception to 15th June 2022). Relevant conference proceedings (2020–2022) were also reviewed. Following feasibility assessment to verify network connectivity at an overall level, outcome specific networks were prepared. Bayesian network meta-analysis (NMA) was performed (using R version 4.2.1) to determine the relative efficacy of various treatments for cUTI/AP, including cefepime + enmetazobactam. Convergence was assessed by visual inspection of trace plots. The accuracy of the posterior estimates was assessed using the Monte Carlo error for each parameter. Published study results were included in the synthesis of the relative risk (RR) of efficacy end points, using a logit link with binomial likelihood distribution.

Results: Feasibility assessment was conducted for 40 RCTs identified, to assess the viability of constructing a network of interlinked RCTs. Of those, 28 studies were included in the master NMA network. A fixed effects model (FEM) was selected due to low statistical heterogeneity, according to I^2 values. For composite outcome at test of cure (TOC), ceftolozane + tazobactam, cefepime + enmetazobactam, cefiderocol, levofloxacin and plazomicin demonstrated significantly higher RRs versus carbapenems. For microbiological eradication at TOC, cefepime + enmetazobactam, plazomicin, cefiderocol, fosfomycin, meropenem + vaborbactam and ceftazidime + avibactam demonstrated significantly higher RRs versus carbapenems. RRs for cefepime + enmetazobactam were also significantly higher versus several established and novel treatment options for composite outcome, microbiological eradication and clinical cure.

Conclusion: Against the backdrop of increasing bacterial resistance, these findings suggest that cefepime + enmetazobactam may represent an effective carbapenem-sparing treatment option in patients with cUTI including AP.

Plain language summary

What is this article about? Complicated urinary tract infections (cUTIs) including acute pyelonephritis (AP, kidney infections) have a high risk of treatment failure, requiring longer courses of antibiotic treatment.

The emergence of drug-resistant organisms poses a considerable global challenge in the treatment of patients with cUTIs/AP due to the limited antibiotic options such as carbapenem antibiotics. Although several established and novel antibiotic treatment options are available, direct comparative data is lacking. This article compares the effectiveness of different antibiotic treatments for complicated urinary tract infections (cUTIs) and acute pyelonephritis (kidney infections). The study performed a systematic review of randomized clinical trials and used a statistical method called network meta-analysis to compare multiple treatments across the identified individual studies.

What were the results? For overall treatment success, several antibiotics such as cefepime + enmetazobactam, ceftolozane + tazobactam, cefiderocol, levofloxacin or plazomicin performed better than standard carbapenem antibiotics. While for full elimination of the bacterial infection from the urine, cefepime + enmetazobactam, plazomicin, cefiderocol, fosfomycin, meropenem + vaborbactam and ceftazidime + avibactam were more effective than carbapenems. Cefepime + enmetazobactam showed considerably better results than several established and newer treatments for overall success, bacterial elimination and clinical cure.

What do the results of the study mean? The findings suggest that some newer antibiotic treatments, particularly cefepime + enmetazobactam, may be more effective than standard carbapenem antibiotics for treating cUTIs and APs (kidney infections). This is important because it provides more treatment options for patients and healthcare providers, especially as bacteria are becoming resistant to commonly used antibiotics. The study concludes that cefepime + enmetazobactam could be an effective alternative to carbapenems, potentially helping to reduce overuse of these last-resort antibiotics and combat the growing problem of antibiotic resistance.

Shareable abstract: New network #meta-analysis shows cefepime + enmetazobactam outperforms several #antibiotics for treating complicated #UTIs, including #carbapenems. Could be an effective carbapenem-sparing option against #drug-resistant #infections. #AntibioticResistance #UTI

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Keywords: acute pyelonephritis • carbapenem • cefepime-enmetazobactam • complicated urinary tract infection • network meta-analysis • systematic literature review • treatment options

Urinary tract infections (UTIs) are among the most common bacterial infections [1,2]. From a clinical perspective, any UTI which occurs in immunocompromised patients, males, pregnant patients and those associated with fevers, stones, sepsis, urinary obstruction, catheters, or involving the kidneys are considered complicated UTIs (cUTIs) [3,4]. Compared with uncomplicated UTIs, cUTIs, including acute pyelonephritis (AP), present with significant morbidity, are associated with higher risks of treatment failure and of developing sepsis and typically require longer courses of treatment or alternative antibiotics [3]. Consequently, cUTIs represent a leading cause of morbidity, mortality and excessive healthcare costs [4]. cUTI can also arise as a nosocomial complication which is an important focus for prevention among hospitalized patients; but regardless of whether community-onset or hospital-onset, cUTIs place a significant burden on the healthcare system [5]. Optimal antimicrobial therapy for cUTIs is dependent on several factors including the severity of illness, presence of risk factors for cUTIs, susceptibility testing and local antimicrobial resistance patterns [3,6,7].

Due to the widespread use of antibiotics globally, antibiotic resistance threatens to undermine the current treatment strategy. The emergence of drug-resistant organisms represents a considerable challenge in the treatment of patients with cUTIs, and has limited antibiotic options for treating cUTIs caused by multidrug-resistant (MDR) organisms [8]. As such, there is an increasing need for the use of second- and third-line antibiotics as well as “last resort” antibiotics such as carbapenems to treat cUTIs. In response to this growing unmet need, a number of novel antibiotics and combination approaches to treatment have been investigated [3,6]. Among those emerging treatment options is cefepime + enmetazobactam, which secured regulatory approvals from the FDA and EMA in 2024, for adult patients with cUTIs, including pyelonephritis, after demonstrating superior efficacy to piperacillin + tazobactam in a phase III clinical trial [9,10,11].

Although several different treatment options exist for patients with cUTI, direct comparative evidence is scarce. Limited head-to-head clinical trials are available to inform treatment decisions, and there remains considerable

uncertainty regarding choice of regimens between patient subgroups. The primary objective of this study was to compare treatment alternatives with cefepime + enmetazobactam in terms of overall response rate, clinical cure and microbiological eradication. Therefore, the aim of this network meta-analysis (NMA) was to assess the relative efficacy of various treatment options compared with carbapenems and, cefepime + enmetazobactam compared with established and novel treatment options, for patients with cUTI including AP.

Materials & methods

Systematic literature review

A systematic literature review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines, utilizing a pre-defined search strategy aligned with the study protocol (Supplementary Table 1A–C). The review encompassed searches of Embase® (<https://www.embase.com/>), Cochrane and MEDLINE® In-Process (<https://pubmed.ncbi.nlm.nih.gov/>), electronic databases from their inception through 15 July 2022, to identify the clinical studies providing efficacy data for patients with cUTIs, including AP. The key search terms used included ‘urinary tract infections’, ‘UTI’, ‘bacteriuria’, ‘cystitis’, ‘bladder infection’ and ‘pyuria’. Additionally, the search was limited to journal articles, excluding conference reviews, editorials, letters, notes, reviews and short surveys. Conference proceedings from European Association of Urology, American Urological Association, International Society of Urology, European Society of Intensive Care Medicine, International Congress of Chemotherapy and Infection, European Society of Clinical Microbiology and Infectious Diseases, Infectious Diseases Society of America were also searched (2020–2022). Bibliographic and grey literature searches were also conducted.

Outcomes of interest included composite outcome (overall response rate), clinical cure and microbiological eradication. The Population, Intervention, Comparator, Outcomes, Time frame, Study design (PICOTS) framework guided the inclusion and exclusion criteria. Inclusion criteria consisted of randomized clinical trials conducted in adult patients and published in English. Full details of interventions and outcomes considered are included in Supplementary Table 2. Studies were selected by two independent reviewers using a two-step process (title/abstracts, followed by full texts) with discrepancies resolved by a third reviewer.

Variable types were prioritized for data extraction and reporting, and the list of evidence was finalized prior to data extraction aligned to the selection criteria. Evidence from the included studies was extracted into a pre-defined extraction grid, ensuring that data were extracted uniformly across studies. Data were independently extracted by two reviewers, with their results checked and reconciled by a third independent reviewer. All studies were critically appraised, following pre-determined critical appraisal questions/areas for consideration according to the published NICE manufacturer’s single technology appraisal template using Cochrane risk of bias assessment checklist [12].

Feasibility assessment

Feasibility assessment was carried out to assess the network connectivity at an overall level, without considering the inclusion/exclusion criteria, baseline characteristics and outcome availability.

For all the studies connected in the network, inclusion/exclusion criteria, patient baseline characteristics and outcome definitions were compared for qualitative assessment of homogeneity of studies. Aligned to the approach used in previous studies, carbapenem antibiotics were pooled together (including doripenem, ertapenem, imipenem + cilastatin, meropenem) due to similar class-level efficacy compared with other comparators [13,14]. This approach was validated by two clinical experts with relevant experience and subject-matter expertise in the disease area, as well as in the domain of NMA. The clinicians were also consulted with regards to the appropriateness of pooling of dose-ranging studies, definitions of cUTI, microbiological eradication and overall response rate.

Carbapenem was identified as the most common comparator across the evidence base and was selected as the reference. Outcome-specific networks were then prepared. As a part of heterogeneity assessment, statistical heterogeneity was calculated for each outcome using I^2 analyses between the reference arms across trials [15]. We conducted a publication bias assessment, with funnel plots and contour-enhanced funnel plots available in the Supplementary Figures. An examination of these plots indicates the absence of publication bias.

Network meta-analysis

Bayesian NMA is more flexible, allows the inclusion of heterogeneous studies and accounts for uncertainty in the effect sizes and variability of the studies. Therefore, Bayesian NMA was performed to determine the relative efficacy of various cUTI/AP treatment options. NMA was conducted using the summary results reported in study

publications and included the synthesis of the odds ratio (OR) and relative risk (RR) of efficacy end points. The methodological approach used was compliant with the NICE Technical Support Documents 2 and 3 [16,17]. Analyses within the Bayesian framework included a likelihood distribution, a model with parameters and prior distributions for these parameters. In this analysis, a logit link with binomial likelihood distribution was used for efficacy outcomes [18].

A Bayesian approach was also adopted using either a fixed effects model (FEM) or random effects model (REM) and the choice of preferred method was informed by the relative goodness of fit of each model [18]. Vague priors were used for REM. For trials with three arms, multi-arms correction was carried out to adjust for the correlation. FEM was selected due to low statistical heterogeneity and its better fit compared with REM. As deviance information criterion (DIC) values for FEM and REM were also comparable, FEM was preferred over REM for parsimony and interpretability. Inconsistency could not be assessed due to the absence of any closed loops of treatments.

This analysis was performed using R version 4.2.1 [17]. Network connectivity was visually verified by each intervention, represented by a node, connected by a line within the network plot. Homogeneity was assessed using the Cochran Q statistic and the I^2 score (with 95% confidence intervals also calculated). Transitivity assessment entailed a qualitative comparison of the distribution of effect modifiers and their effects on the effect size. In the present study, characteristics like age, gender, performance status, disease staging and disease status have been compared for the purpose of transitivity assessment [19]. To assess the robustness of the results, a sensitivity analysis, including studies that are a source of heterogeneity, was carried out.

Results from the NMA were based on a sufficient number of iterations (in other words, 100,000 iterations) on at least three chains, with a burn-in of 20,000 iterations. Convergence was assessed by visual inspection of trace plots. The accuracy of the posterior estimates was assessed using the Monte Carlo (MC) error for each parameter (Monte Carlo error <1% of the posterior standard deviation or MC error divided by posterior standard deviations should be less than 0.05). The results of the NMA were presented in terms of 'point estimates' (median of posterior) for the comparative treatment effects, along with the 95% credible intervals (95% CrI) in forest plots to rank each treatment strategy for visual and statistical verification [19]. Significance was determined according to the credible intervals observed.

Results

Systematic literature review & feasibility assessment

A total of 9426 records were retrieved through electronic literature searches conducted since inception to 15 July 2022 in Embase® (n = 3446), Cochrane (n = 1046) and MEDLINE® In-Process (n = 4934) databases. A total of 40 randomized controlled trials (RCTs) with data reported in 132 publications were identified as meeting the inclusion criteria for the review (Figure 1 & Supplementary Table 3). Risk of bias assessment was conducted with the Jadad score and the NICE appraisal checklist, and suggested there was low risk of bias across the included studies, aside from blinding (Supplementary Table 4).

The majority of RCTs included in the review were multicenter international (25/40), phase III (17/40) and were published as journal articles (36/40). Randomization was adequate in 25 studies and the method of randomization was unclear in 15 studies. Randomization was mainly conducted using an interactive web response system in adequately randomized studies. Most of the studies (23/40) were double-blind, 15 studies were open-label and for two studies blinding was unclear.

The mean age reported ranged from 38–75.3 years across the studies and majority of the studies (23/27 studies) included a higher proportion of female patients compared with males (mean: 60%, range: 23–96%). Patients were diagnosed with cUTI (n = 33), AP (n = 26), acute uncomplicated pyelonephritis (n = 2) and cUTI with AP (n = 2) across the included studies. Definitions of cUTI and AP varied between studies (Supplementary Table 5).

The most common factors associated with classifying UTIs as complicated were partial obstructive uropathy (15–67%), abnormal urogenital tract 5–67%, males with urinary retention (18–67%), catheterization (1–57%) and a urogenital procedure within prior 7 days (15–76%). *Escherichia coli* was the most common gram-negative bacterium associated with cUTI and AP (range: 24–100%) followed by *Klebsiella pneumoniae* (4–65%). All the studies primarily included patients with normal renal function and mild impairment function and excluded patients with moderate or severe renal impairment function.

Feasibility assessment was carried out using the 40 RCTs identified by the systematic literature review, to assess the viability of constructing a network of interlinked RCTs. Of those studies, 28 studies were ultimately included in the master NMA network (Figure 2). The remaining studies were not connected to the network, and therefore, not

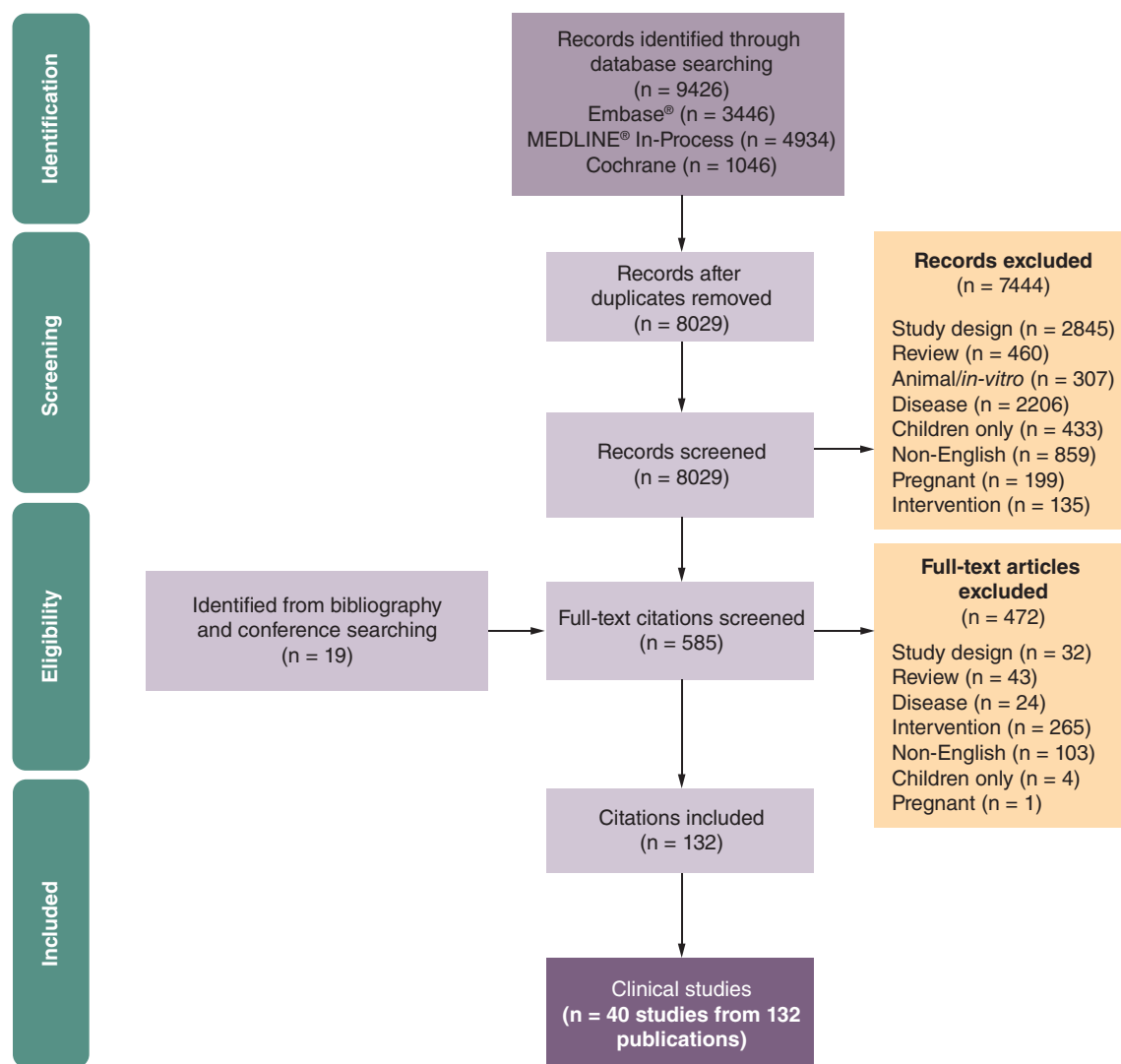
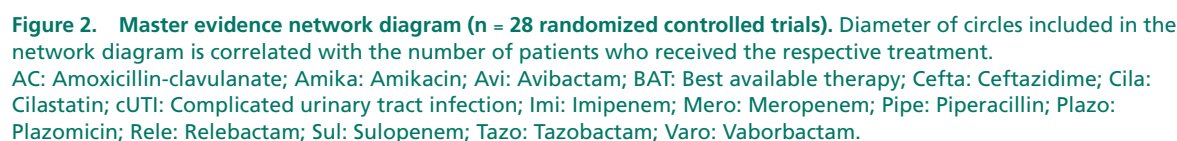


Figure 1. PRISMA flow diagram.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

considered for further analysis. As a part of heterogeneity assessment, statistical heterogeneity has been presented for each outcome using I^2 statistics between the reference arms across trials [15] (Supplementary Table 6). Results from the sensitivity analysis, whereby Seo 2017 was also included marginally increased heterogeneity for some outcomes, but overall, heterogeneity was still low.

Seo 2017 included patients with UTI and scarce details regarding baseline pathogen value, hence, it was not included in the primary analysis due to different inclusion criteria as compared with other studies. However, it was included in a sensitivity analysis due to enrolment of a patient population with a definition of poor prognosis and high severity UTI, relevant for inclusion into the current analysis. Sensitivity analyses were run for outcomes with data available in Seo 2017 [20], in other words, clinical cure at test of cure (TOC) and microbiological eradication at TOC (network diagrams in Supplementary Figures 1–3).

Due to evidence of a connected network, similar inclusion/exclusion criteria, overlapping baseline characteristics, similar outcome definitions across studies and low statistical heterogeneity for all outcomes, an NMA was considered feasible for all the outcomes. Overall, 18 trials contributed to the NMA of clinical cure, 19 trials for microbiological eradication and 16 studies for overall response rate.



Comprehensive statistical analyses were performed comprising of NMA using aggregated data. The end points of interest included composite outcome, clinical cure and microbiological eradication. Herein, the analyses presented are for those that were performed for the overall population using the fixed effects model at TOC (Figures 3–6). A sensitivity analysis was also carried out by including the results from Seo 2017 for clinical cure (TOC) and microbiological eradication (TOC) and results were consistent with the base case results (Supplementary Figure 5). Corresponding analyses at end of treatment (EOT) were generally comparable (Supplementary Figure 4).

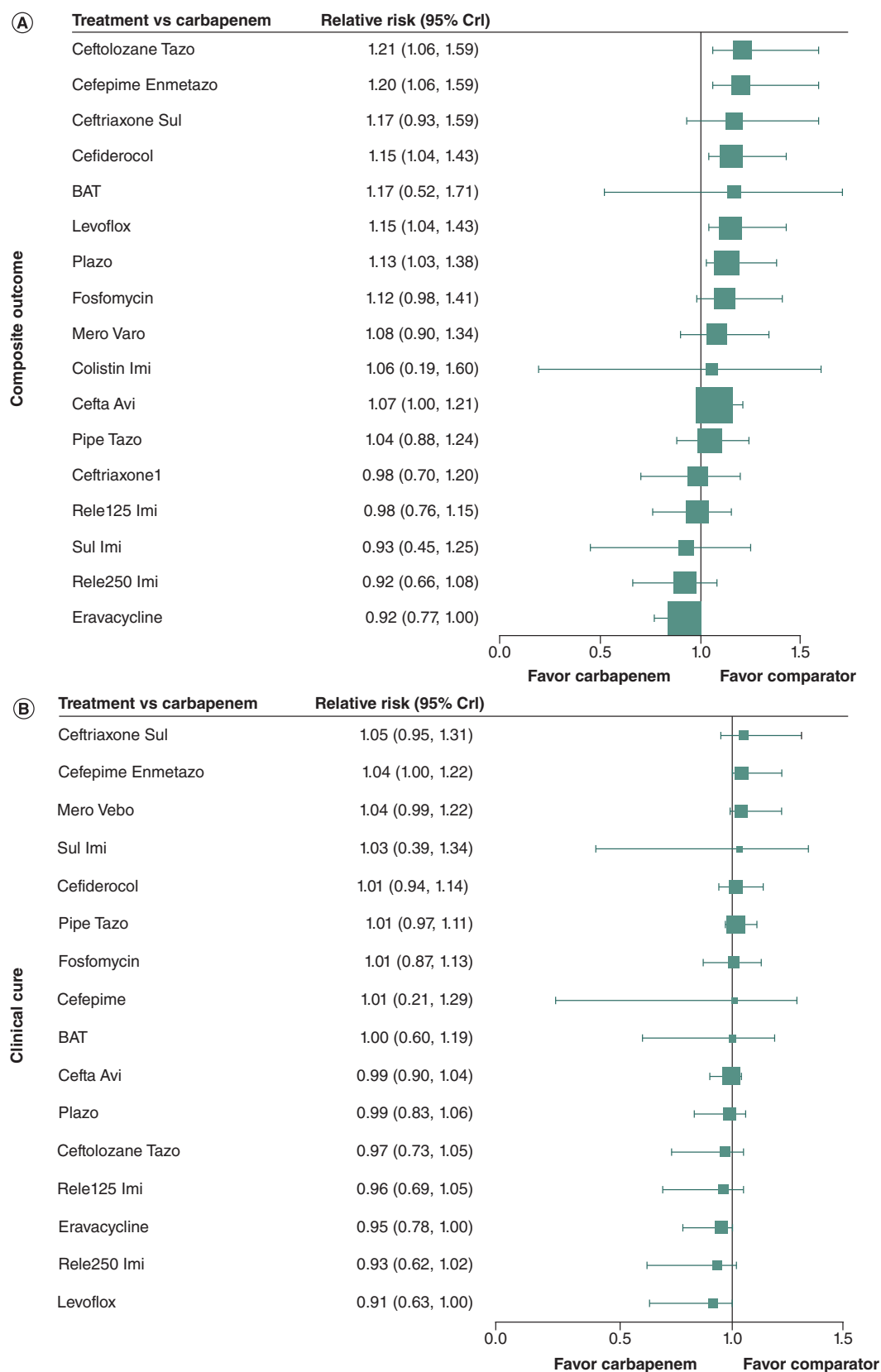


Figure 3. Summary plots. (A) Composite outcome, (B) clinical cure and, (C) microbiological eradication at test of cure (fixed effects model).

Avi: Avibactam; BAT: Best available therapy; Cefta: Ceftazidime; CrI: Credible interval; Enmetazo: Enmetazobactam; FEM: Fixed effects model; HR: Hazard ratio; Imi: Imipenem; Levoflox: Levofloxacin; Mero: Meropenem; Plazo: Plazomicin; Pipe: Piperacillin; Rele: Relebactam; Sul: Sulopenem; Tazo: Tazobactam; TOC: Test of cure; Varo: Vaborbactam; vs: Versus.

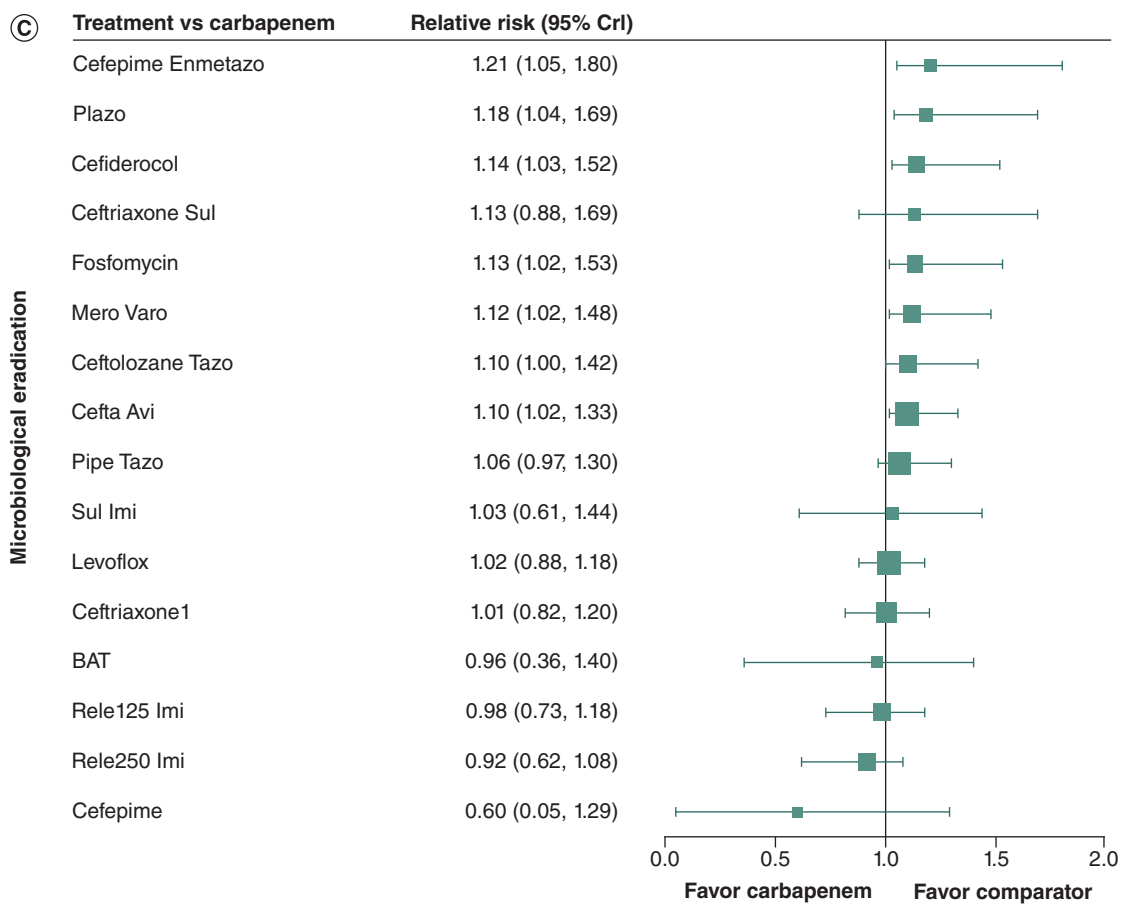


Figure 3. Summary plots (cont.). (A) Composite outcome, (B) clinical cure and, (C) microbiological eradication at test of cure (fixed effects model).
Avi: Avibactam; BAT: Best available therapy; Cefta: Ceftazidime; CrI: Credible interval; Enmetazo: Enmetazobactam; FEM: Fixed effects model; HR: Hazard ratio; Imi: Imipenem; Levoflox: Levofloxacin; Mero: Meropenem; Plazo: Plazomicin; Pipe: Piperacillin; Rele: Relebactam; Sul: Sulopenem; Tazo: Tazobactam; TOC: Test of cure; Varo: Vaborbactam; vs: Versus.

Composite outcome (TOC)

All included treatments versus carbapenem

Rrs for ceftolozane + tazobactam, cefepime + enmetazobactam, cefiderocol, levofloxacin and plazomicin, were significantly higher as compared with carbapenem for composite outcome. Meanwhile, RRs for the remaining comparisons with carbapenem showed no significant differences (Figure 3A).

Cefepime + enmetazobactam versus established & novel treatment options

When compared with established treatment options (carbapenem, levofloxacin, piperacillin + tazobactam, ceftriaxone and cefepime) significantly higher RRs for composite outcome were observed for cefepime + enmetazobactam versus carbapenem, piperacillin + tazobactam and ceftriaxone. RRs for cefepime + enmetazobactam were comparable versus levofloxacin. Comparisons were not available by NMA for cefepime + enmetazobactam versus cefepime. Further, significantly higher RRs for composite outcome were also observed for cefepime + enmetazobactam when compared with some other novel treatments (ceftazidime + avibactam, relebactam 125 mg + imipenem and relebactam 250 mg + imipenem). RRs for cefepime + enmetazobactam for composite outcome were comparable with other novel treatments including meropenem + vaborbactam, cefiderocol and ceftolozane + tazobactam (Figure 4).

Treatment Comparator	Carbapenem	CT	Cefe + Enmetazo	Ceftx + Sul	Cefidocol	BAT	Levo	Piazo	Fos	Mero + Vero	Collis + Imi	Ceftx + Avi	PT	Ceftx	Rele 125 + Imi	Sul + Imi	Rele 250 + Imi	Erava
Carbapenem	1 (1, 1)	1.21 (0.6, 1.59)	1.17 (0.63, 1.59)	1.15 (0.6, 1.43)	1.17 (0.52, 1.71)	1.15 (0.4, 1.43)	0.96 (0.78, 1.26)	1.13 (0.3, 1.38)	1.12 (0.98, 1.41)	1.08 (0.9, 1.34)	1.06 (0.19, 1.6)	1.07 (1, 1.21)	1.04 (0.88, 1.24)	0.98 (0.7, 1.2)	0.98 (0.76, 1.15)	0.93 (0.45, 1.25)	0.92 (0.68, 1.08)	0.92 (0.77, 1)
CT	0.83 (0.63, 0.94)	1 (1, 1)	0.88 (0.72, 1.13)	0.96 (0.82, 1.05)	1 (0.4, 1.2)	0.96 (0.81, 1.05)	0.94 (0.78, 1.03)	0.94 (0.78, 1.03)	0.94 (0.73, 1.05)	0.91 (0.66, 1.02)	0.89 (0.15, 1.16)	0.89 (0.71, 0.98)	0.87 (0.63, 0.98)	0.82 (0.5, 0.97)	0.82 (0.54, 0.96)	0.77 (0.33, 1)	0.76 (0.46, 0.93)	0.76 (0.51, 0.91)
Cefe + Enmetazo	0.53 (0.63, 0.94)	1 (0.88, 1.14)	0.59 (0.72, 1.15)	0.96 (0.82, 1.07)	1 (0.4, 1.22)	0.96 (0.81, 1.07)	0.94 (0.78, 1.04)	0.94 (0.78, 1.04)	0.94 (0.73, 1.05)	0.91 (0.66, 1.03)	0.89 (0.15, 1.17)	0.89 (0.71, 0.98)	0.87 (0.63, 0.98)	0.82 (0.51, 0.98)	0.82 (0.54, 0.96)	0.77 (0.33, 1)	0.76 (0.47, 0.94)	0.76 (0.52, 0.92)
Ceftx + Sul	0.66 (0.63, 1.07)	1.02 (0.68, 1.4)	1.01 (0.67, 1.39)	1 (1, 1)	1.01 (0.42, 1.43)	0.96 (0.8, 1.3)	0.96 (0.78, 1.26)	0.96 (0.78, 1.26)	0.96 (0.74, 1.27)	0.93 (0.67, 1.22)	0.91 (0.15, 1.33)	0.91 (0.71, 1.17)	0.9 (0.64, 1.16)	0.84 (0.51, 1.1)	0.84 (0.55, 1.09)	0.79 (0.34, 1.11)	0.79 (0.47, 1.02)	0.79 (0.52, 1)
Cefidocol	0.67 (0.7, 0.96)	1.04 (0.55, 1.22)	1.02 (0.77, 1.23)	1 (1, 1)	1.03 (0.43, 1.31)	1 (0.87, 1.13)	0.98 (0.85, 1.09)	0.98 (0.85, 1.09)	0.98 (0.79, 1.12)	0.95 (0.72, 1.08)	0.93 (0.16, 1.25)	0.93 (0.78, 1.01)	0.91 (0.68, 1.03)	0.85 (0.55, 1.01)	0.85 (0.59, 0.99)	0.8 (0.36, 1.04)	0.8 (0.51, 0.95)	0.79 (0.57, 0.93)
BAT	0.66 (0.58, 0.94)	1 (0.83, 2.5)	1 (0.62, 2.49)	0.97 (0.76, 2.35)	1 (1, 1)	0.97 (0.75, 2.34)	0.95 (0.77, 2.38)	0.95 (0.77, 2.38)	0.95 (0.7, 2.27)	0.92 (0.64, 2.17)	0.92 (0.16, 2.13)	0.91 (0.65, 2.11)	0.9 (0.6, 2.05)	0.85 (0.49, 1.9)	0.85 (0.52, 1.9)	0.8 (0.33, 1.9)	0.8 (0.45, 1.76)	0.79 (0.48, 1.75)
Levo	0.67 (0.7, 0.96)	1.04 (0.55, 1.24)	1.03 (0.77, 1.25)	1 (0.89, 1.14)	1.04 (0.43, 1.33)	1 (1, 1)	0.98 (0.85, 1.11)	0.98 (0.85, 1.11)	0.98 (0.8, 1.14)	0.95 (0.72, 1.1)	0.93 (0.16, 1.27)	0.93 (0.78, 1.03)	0.92 (0.68, 1.04)	0.86 (0.55, 1.02)	0.86 (0.59, 1)	0.81 (0.36, 1.05)	0.8 (0.51, 0.96)	0.8 (0.57, 0.93)
Piazo	0.89 (0.73, 0.97)	1.06 (0.57, 1.38)	1.04 (0.79, 1.29)	1.02 (0.91, 1.18)	1.05 (0.44, 1.37)	1.02 (0.9, 1.18)	1 (1, 1)	1 (1, 1)	0.97 (0.74, 1.12)	0.95 (0.65, 1.3)	0.95 (0.16, 1.3)	0.95 (0.81, 1.05)	0.93 (0.71, 1.06)	0.87 (0.57, 1.04)	0.87 (0.61, 1.01)	0.82 (0.37, 1.07)	0.81 (0.53, 0.98)	0.81 (0.59, 0.94)
Fos	0.89 (0.71, 1.02)	1.06 (0.56, 1.37)	1.04 (0.79, 1.36)	1.02 (0.9, 1.26)	1.05 (0.44, 1.44)	1.02 (0.88, 1.26)	1 (0.86, 1.22)	1 (0.86, 1.22)	1 (1, 1)	0.97 (0.74, 1.19)	0.95 (0.16, 1.35)	0.95 (0.79, 1.12)	0.93 (0.71, 1.12)	0.85 (0.57, 1.08)	0.85 (0.61, 1.08)	0.82 (0.37, 1.11)	0.82 (0.53, 1.01)	0.82 (0.59, 0.97)
Mero + Vero	0.93 (0.75, 1.1)	1.1 (0.96, 1.51)	1.1 (0.97, 1.51)	1.08 (0.82, 1.49)	1.08 (0.46, 1.58)	1.05 (0.91, 1.39)	1.03 (0.89, 1.35)	1.03 (0.89, 1.35)	1.03 (0.84, 1.36)	1 (1, 1)	0.98 (0.17, 1.47)	0.98 (0.82, 1.23)	0.97 (0.74, 1.22)	0.91 (0.6, 1.16)	0.91 (0.64, 1.14)	0.86 (0.39, 1.19)	0.85 (0.56, 1.07)	0.85 (0.62, 1.03)
Collis + Imi	0.95 (0.63, 0.93)	1.13 (0.86, 0.78)	1.12 (0.86, 0.74)	1.1 (0.75, 0.65)	1.08 (0.47, 0.37)	1.08 (0.79, 0.63)	1.06 (0.77, 0.61)	1.06 (0.77, 0.61)	1.05 (0.74, 0.61)	1.02 (0.68, 0.62)	1 (1, 1)	1 (0.7, 0.72)	0.99 (0.65, 0.54)	0.94 (0.54, 0.51)	0.94 (0.56, 0.51)	0.9 (0.37, 0.72)	0.89 (0.48, 0.7)	0.88 (0.53, 0.69)
Ceftx + Avi	0.94 (0.63, 1)	1.12 (0.62, 1.41)	1.12 (0.62, 1.41)	1.09 (0.6, 1.42)	1.1 (0.47, 1.52)	1.07 (0.97, 1.29)	1.05 (0.85, 1.24)	1.05 (0.85, 1.24)	1.05 (0.89, 1.27)	1.02 (0.82, 1.21)	1 (0.17, 1.43)	1 (1, 1)	0.98 (0.79, 1.13)	0.92 (0.63, 1.1)	0.92 (0.68, 1.07)	0.87 (0.4, 1.15)	0.86 (0.59, 1.02)	0.86 (0.67, 0.97)
PT	0.96 (0.81, 1.19)	1.15 (1.02, 1.59)	1.14 (1.01, 1.58)	1.1 (0.98, 1.45)	1.12 (0.48, 1.66)	1.09 (0.96, 1.44)	1.07 (0.94, 1.4)	1.07 (0.94, 1.4)	1.07 (0.89, 1.42)	1.04 (0.82, 1.35)	1.02 (0.18, 1.55)	1.02 (0.89, 1.28)	1 (1, 1)	0.94 (0.64, 1.2)	0.94 (0.69, 1.17)	0.89 (0.41, 1.23)	0.88 (0.6, 1.1)	0.88 (0.67, 1.04)
Ceftx	1.02 (0.84, 1.42)	1.23 (1.03, 1.99)	1.22 (1.02, 1.98)	1.19 (0.91, 1.94)	1.18 (0.53, 2.03)	1.17 (0.96, 1.92)	1.15 (0.96, 1.78)	1.14 (0.93, 1.77)	1.14 (0.93, 1.77)	1.1 (0.86, 1.67)	1.07 (0.2, 1.86)	1.08 (0.91, 1.89)	1.06 (0.83, 1.57)	1 (1, 1)	1 (0.73, 1.44)	0.95 (0.45, 1.47)	0.94 (0.64, 1.33)	0.94 (0.71, 1.28)
Rele 125 + Imi	1.02 (0.87, 1.31)	1.23 (1.04, 1.86)	1.22 (1.04, 1.86)	1.19 (0.92, 1.83)	1.18 (0.53, 1.93)	1.17 (1, 1.7)	1.15 (0.96, 1.64)	1.14 (0.95, 1.65)	1.14 (0.95, 1.65)	1.1 (0.88, 1.57)	1.07 (0.2, 1.78)	1.09 (0.94, 1.49)	1.06 (0.85, 1.46)	1 (0.69, 1.28)	1 (1, 1)	0.94 (0.45, 1.4)	0.94 (0.65, 1.25)	0.94 (0.73, 1.19)
Sul + Imi	1.08 (0.8, 0.8, 2.24)	1.31 (1, 3.05)	1.27 (0.9, 2.94)	1.25 (0.96, 2.81)	1.25 (0.55, 3)	1.24 (0.95, 2.81)	1.22 (0.93, 2.72)	1.22 (0.93, 2.72)	1.21 (0.9, 2.72)	1.17 (0.84, 2.58)	1.11 (0.21, 2.67)	1.15 (0.87, 2.49)	1.13 (0.81, 2.42)	1.06 (0.68, 2.24)	1.06 (0.71, 2.22)	1 (1, 1)	1 (0.63, 2.03)	1 (0.68, 2)
Rele 250 + Imi	1.09 (0.92, 1.51)	1.32 (1.07, 2.16)	1.27 (0.98, 2.11)	1.26 (1.04, 1.96)	1.26 (0.57, 2.22)	1.25 (1.04, 1.96)	1.23 (1.03, 1.89)	1.23 (1.03, 1.89)	1.22 (0.99, 1.9)	1.18 (0.93, 1.8)	1.13 (0.21, 2.03)	1.16 (0.88, 1.7)	1.13 (0.91, 1.67)	1.06 (0.75, 1.57)	1.06 (0.8, 1.53)	1.01 (0.49, 1.58)	1 (1, 1)	1 (0.79, 1.35)
Erava	1.09 (1, 1.29)	1.32 (1.1, 1.95)	1.27 (1.01, 1.92)	1.26 (1.08, 1.76)	1.26 (0.57, 2.05)	1.25 (1.07, 1.75)	1.23 (1.06, 1.69)	1.23 (1.06, 1.69)	1.22 (1.03, 1.71)	1.18 (0.98, 1.62)	1.13 (0.21, 1.89)	1.16 (0.84, 1.49)	1.13 (0.96, 1.49)	1.06 (0.78, 1.42)	1.06 (0.84, 1.37)	1 (0.5, 1.46)	1 (0.74, 1.27)	1 (1, 1)

Figure 4. Relative risk (95% credible interval) for composite outcome at test of cure (fixed effects model). The green-highlighted and purple sections of the league table are inverse of each other, as they represent the same comparisons, only reversed. All the figures given in the table are results of treatment vs comparator. All studies included in network meta-analysis have equal dosages.

Avi: Avibactam; BAT: Best available therapy; Cefe: Cefepime; Cefta: Ceftazidime; Ceftx: Ceftriaxone; CT: Ceftiozane + Tazobactam; Collis: Cila: Cilastatin; Colistin; Cri: Credible interval; Enmetazo: Enmetazobactam; Erava: Eravacycline; FEM: Fixed effects model; Fos: Fosfomicin; HR: Hazard ratio; Imi: Imipenem; Levo: Levofloxacin; Mero: Meropenem; Plazo: Plazomicin; PT: Piperacillin + Tazobactam; Rele: Relebactam; Sul: Sulopenem; Vero: Vaborbactam.

Treatment Comparator	Carbapenem	Ceftx + Sul	Cefe + Emmezax	Mero + Vero	Sul + Imi	Cefiderocol	PT	Fos	Cefe	BAT	Ceftx + Avi	Piazo	CT	Rele 125 + Imi	Erava	Rele250 + Imi	Levo
Carbapenem	Carbapenem	1.05 (0.95, 1.31)	1.04 (1, 1.22)	1.04 (0.99, 1.22)	1.03 (0.38, 1.34)	1.02 (0.94, 1.14)	1.01 (0.97, 1.11)	1.01 (0.87, 1.13)	1.01 (0.21, 1.29)	1 (0.6, 1.19)	0.99 (0.9, 1.04)	0.99 (0.83, 1.06)	0.97 (0.73, 1.05)	0.98 (0.69, 1.05)	0.95 (0.78, 1)	0.93 (0.62, 1.02)	0.97 (0.63, 1)
Ceftx + Sul	Ceftx + Sul	0.95 (0.76, 1.05)	0.99 (0.85, 1.15)	0.99 (0.85, 1.15)	1 (0.35, 1.2)	0.97 (0.78, 1.1)	0.97 (0.79, 1.09)	0.96 (0.72, 1.08)	0.97 (0.19, 1.16)	0.95 (0.52, 1.1)	0.94 (0.72, 1.05)	0.94 (0.68, 1.05)	0.92 (0.6, 1.03)	0.91 (0.57, 1.03)	0.9 (0.62, 1)	0.88 (0.51, 1.01)	0.87 (0.51, 0.99)
Cefe + Emmezax	Cefe + Emmezax	0.96 (0.82, 1)	1 (0.91, 1.12)	1 (0.9, 1.1)	1.01 (0.36, 1.19)	0.98 (0.83, 1.05)	0.96 (0.85, 1.04)	0.97 (0.78, 1.05)	0.98 (0.19, 1.19)	0.96 (0.54, 1.06)	0.96 (0.77, 1.01)	0.95 (0.72, 1.01)	0.93 (0.64, 1.01)	0.92 (0.6, 1.01)	0.91 (0.66, 0.99)	0.89 (0.54, 0.98)	0.87 (0.54, 0.96)
Mero + Vero	Mero + Vero	0.96 (0.82, 1.01)	1 (0.91, 1.12)	1 (0.9, 1.1)	1.01 (0.36, 1.19)	0.98 (0.83, 1.05)	0.96 (0.85, 1.04)	0.97 (0.77, 1.06)	0.98 (0.2, 1.17)	0.96 (0.54, 1.09)	0.96 (0.77, 1.01)	0.95 (0.73, 1.02)	0.93 (0.64, 1.01)	0.92 (0.6, 1.01)	0.91 (0.66, 0.99)	0.89 (0.54, 1)	0.88 (0.54, 0.96)
Sul + Imi	Sul + Imi	0.97 (0.75, 2.58)	1 (0.84, 2.88)	0.99 (0.83, 2.8)	1.01 (0.36, 1.19)	0.98 (0.77, 2.66)	0.96 (0.78, 2.66)	0.97 (0.72, 2.6)	0.98 (0.21, 2.51)	0.97 (0.54, 2.52)	0.96 (0.72, 2.54)	0.96 (0.68, 2.5)	0.94 (0.61, 2.4)	0.94 (0.56, 2.37)	0.93 (0.62, 2.34)	0.91 (0.52, 2.24)	0.9 (0.52, 2.19)
Cefiderocol	Cefiderocol	0.99 (0.88, 1.07)	1.03 (0.91, 1.28)	1.02 (0.94, 1.21)	1.02 (0.38, 1.3)	1 (0.8, 1.11)	1 (0.9, 1.12)	0.99 (0.82, 1.13)	1 (0.2, 1.26)	0.98 (0.58, 1.17)	0.98 (0.83, 1.07)	0.97 (0.78, 1.07)	0.95 (0.69, 1.05)	0.94 (0.65, 1.05)	0.94 (0.72, 1.01)	0.92 (0.58, 1.02)	0.9 (0.58, 1)
PT	PT	0.99 (0.9, 1.03)	1.03 (0.92, 1.26)	1.02 (0.95, 1.18)	1.02 (0.38, 1.28)	1 (0.86, 1.11)	PT	0.99 (0.82, 1.1)	1 (0.21, 1.24)	0.99 (0.58, 1.15)	0.98 (0.85, 1.04)	0.97 (0.79, 1.05)	0.95 (0.69, 1.04)	0.95 (0.65, 1.04)	0.94 (0.72, 1)	0.92 (0.6, 1.01)	0.9 (0.59, 0.99)
Fos	Fos	0.99 (0.89, 1.16)	1.04 (0.92, 1.38)	1.03 (0.95, 1.31)	1.03 (0.38, 1.39)	1.01 (0.88, 1.23)	1.01 (0.91, 1.21)	1.01 (0.87, 1.19)	1.01 (0.21, 1.33)	0.99 (0.59, 1.24)	0.98 (0.84, 1.15)	0.98 (0.79, 1.14)	0.96 (0.7, 1.12)	0.96 (0.66, 1.11)	0.95 (0.73, 1.06)	0.93 (0.6, 1.07)	0.91 (0.56, 1.03)
Cefe	Cefe	0.99 (0.77, 4.73)	1.03 (0.68, 5.27)	1.02 (0.87, 5.14)	1.02 (0.4, 4.87)	1 (0.8, 4.88)	1 (0.81, 4.88)	0.99 (0.75, 4.77)	Cefe	0.99 (0.57, 4.58)	0.98 (0.74, 4.65)	0.98 (0.71, 4.58)	0.97 (0.64, 4.38)	0.96 (0.61, 4.31)	0.96 (0.65, 4.28)	0.94 (0.55, 4.09)	0.93 (0.55, 3.98)
BAT	BAT	1 (0.84, 1.66)	1.05 (0.91, 1.92)	1.04 (0.92, 1.85)	1.03 (0.4, 1.85)	1.02 (0.86, 1.74)	1.01 (0.87, 1.79)	1.01 (0.81, 1.7)	1.01 (0.22, 1.75)	BAT	1 (0.81, 1.64)	0.99 (0.77, 1.62)	0.98 (0.69, 1.55)	0.97 (0.7, 1.09)	0.96 (0.71, 1.5)	0.95 (0.6, 1.46)	0.95 (0.6, 1.4)
Ceftx + Avi	Ceftx + Avi	1.01 (0.96, 1.11)	1.06 (0.95, 1.38)	1.05 (0.99, 1.29)	1.04 (0.4, 1.47)	1.03 (0.94, 1.2)	1.02 (0.86, 1.18)	1.01 (0.87, 1.19)	1.02 (0.22, 1.34)	1.01 (0.61, 1.24)	Ceftx + Avi	1 (0.84, 1.12)	0.98 (0.74, 1.09)	0.97 (0.7, 1.15)	0.97 (0.78, 1.03)	0.94 (0.63, 1.05)	0.92 (0.64, 1.01)
Piazo	Piazo	1.01 (0.94, 1.2)	1.07 (0.95, 1.47)	1.05 (0.98, 1.38)	1.04 (0.4, 1.47)	1.03 (0.93, 1.29)	1.02 (0.85, 1.27)	1.02 (0.87, 1.26)	1.02 (0.22, 1.41)	1.01 (0.62, 1.3)	1.02 (0.91, 1.35)	1.02 (0.87, 1.34)	0.98 (0.75, 1.16)	0.98 (0.73, 1.28)	0.99 (0.61, 1.22)	0.97 (0.67, 1.22)	0.95 (0.65, 1.06)
CT	CT	1.03 (0.95, 1.37)	1.08 (1, 1.57)	1.08 (0.99, 1.57)	1.06 (0.42, 1.64)	1.05 (0.95, 1.46)	1.05 (0.97, 1.44)	1.04 (0.9, 1.43)	1.03 (0.23, 1.57)	1.03 (0.65, 1.45)	1.02 (0.91, 1.35)	1.02 (0.87, 1.42)	0.98 (0.74, 1.16)	0.98 (0.73, 1.28)	0.99 (0.61, 1.29)	0.97 (0.67, 1.22)	0.95 (0.67, 1.16)
Rele 125 + Imi	Rele 125 + Imi	1.04 (0.95, 1.45)	1.08 (0.99, 1.66)	1.08 (0.99, 1.66)	1.07 (0.42, 1.73)	1.06 (0.95, 1.54)	1.06 (0.96, 1.53)	1.05 (0.9, 1.51)	1.04 (0.23, 1.64)	1.03 (0.65, 1.52)	1.03 (0.91, 1.43)	1.02 (0.87, 1.42)	0.98 (0.75, 1.16)	0.98 (0.73, 1.28)	0.99 (0.61, 1.29)	0.97 (0.67, 1.22)	0.95 (0.67, 1.16)
Erava	Erava	1.05 (1, 1.29)	1.11 (1, 1.62)	1.1 (1.01, 1.52)	1.08 (0.45, 1.62)	1.07 (0.99, 1.4)	1.07 (1, 1.38)	1.05 (0.94, 1.37)	1.05 (0.23, 1.55)	1.04 (0.67, 1.42)	1.04 (0.97, 1.48)	1.03 (0.92, 1.28)	1.01 (0.85, 1.24)	1.01 (0.77, 1.23)	0.99 (0.81, 1.29)	0.98 (0.67, 1.28)	0.96 (0.68, 1.22)
Rele250 + Imi	Rele250 + Imi	1.07 (0.98, 1.61)	1.13 (1, 1.86)	1.12 (1.01, 1.85)	1.1 (0.45, 1.91)	1.09 (0.98, 1.71)	1.09 (0.99, 1.7)	1.08 (0.93, 1.67)	1.08 (0.24, 1.8)	1.06 (0.68, 1.66)	1.06 (0.95, 1.58)	1.05 (0.91, 1.56)	1.03 (0.82, 1.5)	1.02 (0.78, 1.48)	1.02 (0.65, 1.42)	0.99 (0.72, 1.33)	0.99 (0.72, 1.33)
Levo	Levo	1.1 (1, 1.59)	1.16 (1.01, 1.96)	1.14 (1.02, 1.85)	1.11 (0.46, 1.93)	1.11 (1, 1.7)	1.11 (1.01, 1.69)	1.1 (0.97, 1.66)	1.08 (0.25, 1.82)	1.07 (0.71, 1.68)	1.08 (0.99, 1.56)	1.07 (0.95, 1.55)	1.05 (0.86, 1.48)	1.04 (0.82, 1.47)	1.04 (0.9, 1.39)	1.01 (0.75, 1.38)	0.99 (0.72, 1.33)

Figure 5. Relative risk (95%, credible interval) for clinical cure at test of cure (fixed effects model). The green-highlighted and purple sections of the league table are inverse of each other, as they represent the same comparisons, only reversed. All the figures given in the table are results of treatment vs comparator.
Avi: Avibactam; BAT: Best available therapy; Cefe: Cefepime; Cefta: Ceftazidime; Cefcx: Ceftriaxone; CT: Ceftriaxone + Tazobactam; Crl: Credible interval; Enmetazo: Enmetazobactam; Erava: Eravacycline; FEM: fixed effects model; Fos: Fosfomycin; HR: Hazard ratio; Imi: Imipenem; Levo: Levofloxacin; Mero: Meropenem; Piazo: Plazomicin; PT: Piperacillin + Tazobactam; Rele: Relebactam; Sul: Sulopenem; TOC: Test of cure; Voro: Vaborbactam.

Treatment	Comparator	Reliability															Cite	
		Carbapenem	Cefix + Enmetaz	Plazo	Cefiderocol	Cefix + Sul	Fos	Mero Vabo	CT	Cefix + Avl	PT	Sul + Imi + Cfm	Levo	Cefix	DAT	Reli 125 + Imi		Reli30 + Imi
Carbapenem	Carbapenem	1 (1, 1)	1.21 (1.05, 1.8)	1.18 (1.04, 1.69)	1.14 (1.03, 1.52)	1.13 (0.88, 1.69)	1.13 (1.02, 1.53)	1.12 (1.02, 1.48)	1.1 (1, 1.42)	1.1 (1.02, 1.33)	1.07 (0.97, 1.3)	1.03 (0.81, 1.44)	1.02 (0.88, 1.18)	1.01 (0.82, 1.2)	0.96 (0.76, 1.4)	0.98 (0.73, 1.18)	0.92 (0.62, 1.08)	0.6 (0.05, 1.3)
		0.83 (0.56, 0.96)	1 (1, 1)	0.98 (0.84, 1.08)	0.95 (0.77, 1.03)	0.97 (0.63, 1.11)	0.95 (0.74, 1.04)	0.94 (0.73, 1.02)	0.94 (0.73, 1.02)	0.92 (0.69, 1.01)	0.89 (0.63, 0.99)	0.87 (0.42, 1.03)	0.85 (0.55, 0.97)	0.84 (0.52, 0.97)	0.8 (0.25, 1.03)	0.81 (0.47, 0.97)	0.75 (0.39, 0.85)	0.49 (0.04, 1.01)
		0.85 (0.59, 0.96)	1.02 (0.93, 1.19)	1 (1, 1)	0.97 (0.81, 1.07)	0.98 (0.66, 1.17)	0.97 (0.77, 1.08)	0.96 (0.76, 1.06)	0.96 (0.76, 1.06)	0.94 (0.72, 1.04)	0.93 (0.75, 1.01)	0.91 (0.67, 1)	0.89 (0.44, 1.06)	0.87 (0.59, 0.98)	0.86 (0.55, 0.98)	0.82 (0.26, 1.06)	0.83 (0.49, 0.96)	0.77 (0.41, 0.96)
Cefiderocol	Cefiderocol	0.88 (0.66, 0.97)	1.05 (0.86, 1.3)	1.03 (0.94, 1.23)	1 (1, 1)	1.01 (0.71, 1.26)	0.99 (0.83, 1.13)	0.97 (0.79, 1.1)	0.97 (0.79, 1.1)	0.97 (0.82, 1.05)	0.94 (0.73, 1.04)	0.92 (0.47, 1.12)	0.9 (0.65, 0.99)	0.89 (0.6, 1)	0.84 (0.28, 1.12)	0.85 (0.54, 1)	0.8 (0.45, 0.97)	0.52 (0.04, 1.08)
		0.88 (0.59, 1.14)	1.04 (0.8, 1.59)	1.02 (0.86, 1.52)	0.99 (0.79, 1.42)	1 (1, 1)	0.99 (0.77, 1.42)	0.98 (0.76, 1.39)	0.97 (0.72, 1.35)	0.96 (0.73, 1.32)	0.94 (0.67, 1.27)	0.92 (0.45, 1.3)	0.9 (0.59, 1.19)	0.89 (0.56, 1.18)	0.84 (0.27, 1.25)	0.87 (0.5, 1.15)	0.8 (0.42, 1.07)	0.52 (0.04, 1.13)
		0.88 (0.66, 0.98)	1.05 (0.97, 1.36)	1.03 (0.93, 1.29)	1 (0.87, 1.2)	1.01 (0.71, 1.3)	1 (1, 1)	0.99 (0.82, 1.18)	0.98 (0.78, 1.14)	0.97 (0.81, 1.1)	0.95 (0.73, 1.08)	0.92 (0.47, 1.16)	0.9 (0.64, 1.02)	0.89 (0.6, 1.03)	0.85 (0.28, 1.14)	0.87 (0.54, 1.02)	0.8 (0.45, 0.88)	0.52 (0.04, 1.09)
Mero Vabo	Mero Vabo	0.89 (0.66, 0.98)	1.06 (0.98, 1.38)	1.04 (0.95, 1.31)	1.01 (0.89, 1.21)	1.02 (0.72, 1.32)	1.01 (0.85, 1.22)	1 (1, 1)	0.99 (0.8, 1.15)	0.98 (0.83, 1.11)	0.96 (0.75, 1.09)	0.93 (0.48, 1.17)	0.91 (0.66, 1.02)	0.9 (0.62, 1.03)	0.86 (0.29, 1.15)	0.88 (0.56, 1.02)	0.81 (0.47, 0.89)	0.53 (0.04, 1.1)
		0.91 (0.7, 1)	1.08 (0.99, 1.46)	1.06 (0.97, 1.38)	1.03 (0.91, 1.27)	1.03 (0.74, 1.39)	1.02 (0.86, 1.28)	1.01 (0.87, 1.25)	1 (1, 1)	0.99 (0.86, 1.16)	0.97 (0.78, 1.13)	0.95 (0.5, 1.22)	0.93 (0.69, 1.06)	0.92 (0.64, 1.06)	0.87 (0.29, 1.19)	0.89 (0.58, 1.05)	0.83 (0.49, 1)	0.54 (0.04, 1.13)
		0.94 (0.77, 1.03)	1.12 (1.02, 1.58)	1.1 (1, 1.49)	1.06 (0.96, 1.36)	1.06 (0.79, 1.5)	1.05 (0.93, 1.37)	1.05 (0.92, 1.33)	1.03 (0.88, 1.25)	1.02 (0.92, 1.23)	1 (1, 1)	0.98 (0.81, 1.09)	0.95 (0.51, 1.2)	0.93 (0.72, 1.02)	0.92 (0.67, 1.03)	0.88 (0.3, 1.18)	0.9 (0.6, 1.03)	0.83 (0.5, 0.99)
Sul + Imi	Sul + Imi	0.97 (0.69, 1.65)	1.15 (0.97, 2.41)	1.13 (0.94, 2.29)	1.09 (0.89, 2.12)	1.09 (0.77, 2.21)	1.08 (0.65, 2.12)	1.07 (0.65, 2.07)	1.06 (0.62, 2)	1.05 (0.63, 1.95)	1.03 (0.77, 1.87)	1.02 (0.58, 1.44)	1 (1, 1)	0.96 (0.65, 1.7)	0.94 (0.32, 1.74)	0.95 (0.6, 1.64)	0.9 (0.51, 1.48)	0.59 (0.05, 1.46)
		0.98 (0.66, 1.13)	1.18 (1.03, 1.81)	1.16 (1.02, 1.7)	1.12 (1.01, 1.55)	1.11 (0.84, 1.69)	1.11 (0.96, 1.55)	1.1 (0.88, 1.51)	1.08 (0.85, 1.45)	1.07 (0.88, 1.39)	1.04 (0.91, 1.34)	1.02 (0.58, 1.44)	1 (1, 1)	0.99 (0.76, 1.23)	0.94 (0.34, 1.4)	0.97 (0.69, 1.2)	0.9 (0.56, 1.1)	0.59 (0.05, 1.28)
		0.99 (0.64, 1.22)	1.19 (1.03, 1.93)	1.17 (1.02, 1.82)	1.13 (1, 1.66)	1.12 (0.85, 1.79)	1.12 (0.97, 1.66)	1.11 (0.97, 1.62)	1.09 (0.94, 1.55)	1.08 (0.97, 1.49)	1.05 (0.8, 1.44)	1.02 (0.59, 1.52)	1.01 (0.81, 1.31)	1 (1, 1)	0.95 (0.35, 1.47)	0.96 (0.69, 1.28)	0.91 (0.59, 1.16)	0.6 (0.05, 1.33)
BAT	BAT	1.04 (0.71, 2.81)	1.26 (0.97, 4.05)	1.23 (0.94, 3.88)	1.18 (0.9, 3.61)	1.19 (0.8, 3.66)	1.18 (0.86, 3.56)	1.17 (0.87, 3.51)	1.15 (0.84, 3.4)	1.14 (0.84, 3.33)	1.11 (0.79, 3.19)	1.07 (0.58, 3.09)	1.06 (0.71, 2.91)	1.05 (0.68, 2.88)	1 (1, 1)	1.02 (0.63, 2.76)	0.98 (0.54, 2.47)	0.66 (0.05, 2.14)
		1.02 (0.65, 1.36)	1.23 (1.03, 2.14)	1.12 (1.02, 2.02)	1.16 (1, 1.84)	1.16 (0.87, 1.98)	1.15 (0.99, 1.85)	1.14 (0.98, 1.8)	1.12 (0.95, 1.73)	1.11 (0.97, 1.66)	1.08 (0.91, 1.6)	1.05 (0.91, 1.67)	1.03 (0.83, 1.45)	1.02 (0.78, 1.45)	0.98 (0.36, 1.59)	1 (1, 1)	0.94 (0.61, 1.27)	0.62 (0.05, 1.41)
		1.09 (0.93, 1.61)	1.33 (1.06, 2.57)	1.3 (1.06, 2.42)	1.25 (1.03, 2.21)	1.24 (0.94, 2.36)	1.25 (1.02, 2.21)	1.23 (1.02, 2.15)	1.21 (1, 2.06)	1.2 (1.01, 1.99)	1.17 (0.96, 1.9)	1.12 (0.88, 1.98)	1.11 (0.91, 1.72)	1.1 (0.88, 1.71)	1.04 (0.4, 1.86)	1.07 (0.79, 1.65)	1 (1, 1)	0.67 (0.06, 1.61)
Reli 125 + Imi	Reli 125 + Imi	1.66 (0.77, 20.4)	2.05 (0.99, 28.36)	2 (0.97, 27.26)	1.93 (0.93, 25.52)	1.92 (0.88, 25.75)	1.9 (0.91, 24.95)	1.86 (0.88, 24.13)	1.85 (0.88, 23.8)	1.79 (0.84, 22.8)	1.69 (0.69, 21.49)	1.69 (0.78, 21.09)	1.67 (0.76, 20.66)	1.51 (0.47, 14.14)	1.61 (0.71, 19.79)	1.5 (0.62, 17.79)	1 (1, 1)	
		1.66 (0.77, 20.4)	2.05 (0.99, 28.36)	2 (0.97, 27.26)	1.93 (0.93, 25.52)	1.92 (0.88, 25.75)	1.9 (0.91, 24.95)	1.86 (0.88, 24.13)	1.85 (0.88, 23.8)	1.79 (0.84, 22.8)	1.69 (0.69, 21.49)	1.69 (0.78, 21.09)	1.67 (0.76, 20.66)	1.51 (0.47, 14.14)	1.61 (0.71, 19.79)	1.5 (0.62, 17.79)	1 (1, 1)	

Figure 6. Relative risk (95% credible interval) for microbiological eradication at test of cure (fixed effects model). The green-highlighted and purple sections of the league table are inverse of each other, as they represent the same comparisons, only reversed. All the figures given in the table are results of treatment vs comparator. All studies included in network meta-analysis have equal dosages.

Abbreviations: BAT: Best available therapy; Cefe: Cefepime; Cefta: Ceftazidime; Ceftx: Ceftioxane; CT: Ceftolozane + Tazobactam; Collis: Colistin; CrI: Credible interval; Avi: Avibactam; BAT: Best available therapy; Cefe: Cefepime; Cefta: Ceftazidime; Ceftx: Ceftioxane; CT: Ceftolozane + Tazobactam; Collis: Colistin; CrI: Credible interval; Enmetazo: Enmetazobactam; Erava: Eravacycline; FEM: Fixed effects model; Fos: Fosfomycin; HR: Hazard ratio; Imi: Imipenem; Levo: Levofloxacin; Mero: Meropenem; Plazo: Plazomicin; PT: Piperacillin + Tazobactam; Rele: Reltebactam; Sul: Sulopenem; Varo: Vaborbactam.

*Clinical cure (TOC)**All included treatments versus carbapenem*

RRs for all treatments versus carbapenem were comparable, indicating no significant difference for clinical cure (Figure 3B).

Cefepime + enmetazobactam versus established & novel treatment options

RRs for clinical cure were generally comparable for cefepime + enmetazobactam compared with established treatment options (carbapenem, levofloxacin, piperacillin + tazobactam, ceftriaxone and cefepime), with significantly higher RRs only observed for the comparison with levofloxacin. Similarly, comparisons of cefepime + enmetazobactam with other novel treatment options for clinical cure generally yielded similar RRs (including vs ceftazidime + avibactam, relebactam 125 mg + imipenem, meropenem + vaborbactam, cefiderocol and ceftolozane + tazobactam). In the comparison with relebactam 250 mg + imipenem, the RR for cefepime + enmetazobactam was significantly higher (Figure 5).

*Microbiological eradication (TOC)**All included treatments versus carbapenem*

RRs for microbiological eradication for cefepime + enmetazobactam, plazomicin, cefiderocol, fosfomycin, meropenem + vaborbactam and ceftazidime + avibactam were significantly higher compared with carbapenem (Figure 3C). Meanwhile, no significant difference was observed in the RRs for other treatments compared with carbapenem.

Cefepime + enmetazobactam versus established & novel treatment options

When compared with established treatment options, RRs for cefepime + enmetazobactam were significantly higher versus carbapenem, levofloxacin, piperacillin + tazobactam and ceftriaxone for microbiological eradication, while RRs were comparable versus cefepime. When considering comparisons against novel treatments, RRs for cefepime + enmetazobactam were significantly higher versus ceftazidime + avibactam, relebactam 125 mg + imipenem and relebactam 250 mg + imipenem for microbiological eradication. RRs for cefepime + enmetazobactam were comparable versus meropenem + vaborbactam, cefiderocol and ceftolozane + tazobactam (Figure 6).

Discussion

UTIs represent one of the most common infections worldwide and are associated with a decrease in the quality of life of patients, as well as substantial clinical and economic burden [1,2]. In response to the growing unmet need among patients with cUTI/AP due to the increased development of MDR organisms, a number of novel therapies have been developed to provide additional treatment options beyond the more established antimicrobials [3].

Appropriate end point selection continues to be an important aspect of establishing clinical benefits among treatments under investigation in clinical trials. Current guidance from the EMA and the US FDA issued in 2022 and 2018, respectively, stipulates that the primary end point for clinical trials in cUTI should include a composite outcome, including both clinical and microbiological outcome criteria [21,22]. These end point specifications were recently validated in a study by Kadry *et al.*, which provided further insights into the importance of microbiological eradication in composite end points, for clinical trials in cUTI [23]. Notably, the analysis reported that the risk of future clinical failure among participants was elevated more than five-times in those who achieved clinical cure but experienced microbiological persistence, with risk of failure increasing over time [23]. As such, composite outcomes including microbiological eradication represent a key consideration for interpretation within the context of this study.

Carbapenems represent one of the cornerstones of treatment for patients with cUTI/AP and were among the most identified therapies among the clinical trials identified from the literature [24]. Although carbapenems represent an effective treatment to combat rising resistance, their use should be reserved to latter lines of therapy, as overuse has contributed to the emergence of carbapenem resistance [6,25,26]. Therefore, identifying effective alternatives that facilitate a carbapenem-sparing approach, or provide additional treatment options for patients with carbapenem resistance remains of paramount importance for public health [26,27]. In the present study, for microbiological eradication at TOC, cefepime + enmetazobactam, plazomicin, cefiderocol, fosfomycin, meropenem + vaborbactam and ceftazidime + avibactam demonstrated significantly higher RRs compared with carbapenems. While for

composite outcome at TOC, ceftolozane + tazobactam, ceftazidime + avibactam, ceftazidime + sulopenem, meropenem + vaborbactam, sulopenem + imipenem, ceftazidime + sulopenem, ceftazidime + sulopenem + vaborbactam, sulopenem + imipenem, ceftazidime + sulopenem + vaborbactam, fosfomycin and ceftazidime showed comparable RRs to carbapenem for clinical cure at TOC. Encouragingly, these findings suggest that among those antimicrobials included in the NMA, several different treatments may yield beneficial outcomes compared with carbapenems. Comparable results were observed by Ezure *et al.*, where no differences in clinical response were observed by NMA between a pooled group of new antibiotic treatments (including ceftazidime + avibactam, ceftazidime + sulopenem, ceftazidime + sulopenem + vaborbactam, sulopenem + imipenem, ceftazidime + sulopenem + vaborbactam, fosfomycin and ceftazidime) versus carbapenems, but microbiological eradication rates were significantly higher in the pooled group versus carbapenems [13]. Meanwhile, in another study, ceftazidime + avibactam has previously been found to demonstrate comparable efficacy to carbapenems in a pair-wise meta-analysis, for infections (including cUTI) caused by *Enterobacteriaceae* [28].

In 2024, ceftazidime + avibactam secured regulatory approvals from both the FDA and EMA, for adult patients with cUTIs, including AP, after demonstrating superior efficacy to piperacillin/tazobactam in a phase III clinical trial [9,10,11]. In the absence of head-to-head data, to help assess the relative efficacy and inform the potential positioning of ceftazidime + avibactam, comparisons were conducted versus other treatment options. When compared with established treatments for cUTIs, ceftazidime + avibactam demonstrated significantly higher RRs versus carbapenem, levofloxacin, piperacillin + tazobactam and ceftazidime for microbiological eradication. Meanwhile, when considering comparisons against novel treatments, ceftazidime + avibactam also demonstrated significantly higher RRs versus ceftazidime + avibactam, relebactam 125 mg + imipenem and relebactam 250 mg + imipenem for microbiological eradication with comparable RRs versus meropenem + vaborbactam, ceftazidime and ceftazidime + tazobactam.

While head-to-head studies providing direct comparative data remain the pinnacle in terms of robustness of evidence, due to the lack of such evidence to date, this study was conducted to help assess the comparative efficacy among currently available treatments. However, the study did include some noteworthy limitations. The potential clinical variation among the included studies and the assumption of transitivity may not be valid. However, as an exhaustive list of the baseline characteristics were not available, it was not possible to compare and ascertain it. Further, the SLR was restricted to English language publications only which may include bias for non-English publications. Overall, the studies identified in the systematic literature review had a low risk of bias, with blinding considered the only potential source of bias, since 16 studies were conducted in an open-label setting. Despite this, publication bias assessment was not required since most studies were non-inferiority trials, and the results were non-significant. Different definitions of cUTI and AP were also used across the different trials, which can have an impact on the outcomes assessed. However, during the validation of the methodology by clinical experts, it was deemed that the variations observed among the studies in terms of disease definitions would not have a significant impact on the findings. Nevertheless, a homogenisation of guidelines is needed, as suggested in a recent consensus study [29]. While merging all types of carbapenems due to their comparable efficacy is an approach previously used and further validated by expert clinicians in this analysis, it resulted in the exclusion of a small number of trials comparing various carbapenems [13,14]. Due to the limited availability of published evidence, some comparisons within the network were supported by only a single study, with some of these studies conducted in small patient populations.

Conclusion

In terms of composite outcome at TOC, ceftazidime + avibactam demonstrated significantly higher RRs compared with carbapenem, ceftazidime + avibactam, piperacillin + tazobactam, ceftazidime, relebactam 125 mg + imipenem, sulbactam + imipenem, eravacycline and relebactam 250 mg + imipenem. Ceftazidime + avibactam also exhibited significantly higher RRs in terms of clinical cure at TOC as compared with carbapenem, ceftolozane + tazobactam, eravacycline, relebactam 250 mg + imipenem and levofloxacin, as well as significantly higher RRs compared with carbapenem, ceftazidime + avibactam, piperacillin + tazobactam, levofloxacin, ceftazidime and relebactam 125 mg + imipenem for microbiological eradication at TOC. In the face of rising multidrug-resistant bacterial infections, these findings suggest that ceftazidime + avibactam may represent an effective carbapenem-sparing treatment option in patients with cUTI/AP and an additional tool to hopefully reduce cUTI/AP-associated morbidity, mortality and healthcare costs.

Summary points

- The study aimed to assess the relative efficacy of various treatment options, including cefepime + enmetazobactam compared with carbapenems for complicated UTIs (cUTIs)/acute pyelonephritis (AP).
- A systematic review identified 40 randomized controlled trials, with 28 studies included in the final network meta-analysis.
- For composite outcome at test of cure (TOC), ceftolozane + tazobactam, cefepime + enmetazobactam, cefiderocol, levofloxacin and plazomicin showed significantly higher relative risks (RRs) compared with carbapenems.
- For microbiological eradication at test of cure, cefepime + enmetazobactam, plazomicin, cefiderocol, fosfomycin, meropenem + vaborbactam and ceftazidime + avibactam demonstrated significantly higher RRs versus carbapenems.
- Cefepime + enmetazobactam showed significantly higher RRs compared with several established and novel treatments for composite outcome, microbiological eradication and clinical cure.
- The findings suggest cefepime + enmetazobactam may be an effective carbapenem-sparing option for treating cUTIs/AP.
- Results were consistent between analyses at TOC and EOT timepoints. Limitations included potential clinical variation between studies and limited head-to-head comparative data for some treatments.
- The study helps assess comparative efficacy among available treatments in the absence of direct head-to-head trials for all options.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2024-0214>

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Competing interests disclosure

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