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MAJOR ARTICLE

Efficacy and Safety of Carbapenems vs New Antibiotics for Treatment of Adult Patients With Complicated Urinary Tract Infections: A Systematic Review and Meta-analysis

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This systematic review and meta-analysis evaluated the clinical efficacy and safety of carbapenems for the treatment of complicated urinary tract infections (cUTIs), with the comparators being new antibiotics evaluated for this indication. We searched 13 electronic databases for published randomized controlled trials (RCTs) and completed and/or ongoing trials. The search terms were developed using the Population, Intervention, Comparison, Outcomes, and Study framework. Pooled efficacy estimates of composite cure (clinical success and microbiological eradication) favored the new antibiotic groups, although this was not statistically significant (risk ratio [RR], 0.91; 95% CI, 0.79–1.04). A pooled estimate examining clinical response alone showed no difference between treatment arms (RR, 1.00; 95% CI, 0.96–1.05), however, new antibiotic treatments were superior to carbapenems for microbiological response (RR, 0.85; 95% CI, 0.79–0.91). New antibiotic treatments demonstrated a superior microbiological response compared with carbapenems in clinical trials of cUTI, despite an absence of carbapenem resistance. However, it is noteworthy that the clinical response and safety profile of new antibiotics were not different from those of carbapenems.

Keywords. carbapenem; complicated urinary tract infections; efficacy and safety; new antibiotics; systematic review and meta-analysis.

Complicated urinary tract infections (cUTIs) occur in individuals with anatomical or functional abnormalities of the urinary tract and often require hospitalization and antibiotics [1]. Risk factors of cUTI are multifaceted and complex and include comorbidities such as diabetes mellitus, pregnancy, aging, urinary tract obstruction, renal failure, indwelling urinary catheter use, renal transplantation, and immunosuppression [2]. Health care acquisition of UTI is also an important risk factor for development of complications [3]. The most common pathogens causing cUTI are the gram-negative bacteria, including *Escherichia coli*, *Klebsiella* spp., *Citrobacter* spp., and *Pseudomonas* spp. [1]. While beta-lactam antibiotics are usually recommended for treatment of infections caused by these bacteria, gram-negative pathogens often develop resistance to cephalosporins and beta-lactam/beta-lactamase inhibitor combinations, mainly by producing various beta-lactamases [4].

Multidrug-resistant (MDR) pathogens, especially gram-negative bacilli, are a worldwide problem [5]. Notably, many of the common pathogens causing cUTIs are frequently MDR in some countries, and there is a foreseen trend of microbiological resistance in urinary pathogens [6]. For these reasons, prescription of adequate antibiotics is critical and increasingly difficult for cUTI. An inappropriate choice of antibiotics may lead to persistence of infection, relapse, or reinfection, and thus increased health care costs from prolonged length of hospital stay [7].

Carbapenems are a class within the beta-lactam family of antibiotics, which are generally an effective treatment for serious infections due to their in vitro activity against the majority of gram-negative bacteria [8] and their proven clinical track record, including against extended-spectrum beta-lactamase (ESBL)–producing organisms [9]. However, the worldwide spread of highly resistant pathogens, including carbapenem-resistant Enterobacteriaceae (CRE), may compromise the efficacy of carbapenems [10]. The urgent need for the development of new antibiotics has been recognized in the global political agenda and is one of the World Health Organization's (WHO's)

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recommendations [11]. However, the development of novel antibiotics has been slowed over the past 30 years [12]. To confront the problem of MDR pathogens, several new antibiotics have been approved by US Food and Drug Administration (FDA) and European Medicines Agency (EMA), while others continue in clinical development [13].

There have been promising results from well-designed randomized controlled trials (RCTs) examining these new antibiotics for serious infections such as cUTIs [13]. However, individual RCT results are often difficult to interpret in everyday clinical practice. Therefore, summative evidence needs to be updated, evaluating the newly approved antibiotics vs their comparators. While several systematic reviews and meta-analyses that have compared the treatment effects between new antibacterial agents and alternative antibiotics are available [14–16], no studies have yet computed summative data of RCTs comparing recently studied antibiotics and carbapenems for cUTI treatment. We therefore conducted a systematic review and meta-analysis of RCTs to evaluate the comparative efficacy and safety of carbapenems and new antibiotic treatments for patients with cUTI.

METHODS

This paper adheres to the PRISMA guideline for reporting systematic reviews and meta-analysis [17]. The protocol of this study was registered with PROSPERO, the International Prospective Register of Systematic Reviews, on April 10, 2019 (registration number CRD42019124987).

Patient Consent Statement

As a meta-analysis, this study does not include factors necessitating patient consent.

Literature Search and Selection Criteria

The search terms were developed according to these Population, Intervention, Comparison, Outcomes, and Study (PICOS) criteria:

- Participants: adult participants (age 18 years and older) with complicated urinary tract infections
- Intervention: carbapenem treatments
- Comparison: new antibiotic treatments (defined as those submitted to the FDA or EMA for approval for the cUTI indication from 2009 to 2019, excluding carbapenems alone or in combination with new beta-lactamase inhibitors)
- Outcomes: efficacy and safety measures, including clinical response, microbiological response, and adverse effects
- Study type: randomized controlled trials

In March 2019, we conducted a systematic literature search in electronic databases, including PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, CINAHL, and MEDLINE. A complementary hand search was also conducted by screening the reference lists of the included articles. ClinicalTrials.gov, ANZCTR (Australian New Zealand Clinical Trials Registry), the WHO website, and Google Scholar were searched to identify completed and ongoing trials. The literature was limited to English and Spanish, and the data to publication within 10 years. The search strategies were discussed with a medical librarian, and the details are listed in Supplementary Appendix 1.

Study Selection

Two reviewers, Y.E. and H.W., independently screened the titles, abstracts, and the full text of selected articles to identify their eligibility according to the inclusion and exclusion criteria (Supplementary Appendix 1). Briefly, eligible trials were all available RCTs that compared carbapenems with any other new antibiotics for the treatment of adult patients (over 18 years old) who were diagnosed with/suspected to have complicated urinary tract infections, including pyelonephritis. Therefore, trials including placebo controls and study populations that included individuals with uncomplicated urinary tract infections, healthy volunteers, women who were pregnant or breastfeeding, individuals obtaining other antibacterial treatments or/and other medical treatments that had the potential to affect intervention outcomes, and individuals with a history of any allergic reaction to any beta-lactam antibiotics were excluded.

Data Extraction

Relevant data from studies eligible for inclusion were extracted by following the Cochrane Handbook for Systematic Reviews of interventions [17]. The following information was extracted and recorded from each selected study: (i) name of author and publication year; (ii) characteristics of study, such as study design, study periods, and sample size; (iii) countries included in the study and characteristics of the participants, including age, sex, and race; (iv) intervention characteristics, including dosage, delivery, and duration of antibiotics; (v) types of outcomes; (vi) pathogens identified at baseline; (vii) subgroup population analyzed in the study; (viii) end points of efficacy. Any conflict was resolved by discussing between all reviewers or/and seeking advice from co-authors. To ensure the reliability of the data, the data were extracted by 2 reviewers independently.

Risk of Bias Assessment

The "risk of bias tool" from the Cochrane Collaboration was used to assess the quality of selected trials by classifying each item separately as low, unclear, or high risk [18]. The assessment items included (i) random sequence generation (selection bias); (ii) allocation concealment (selection bias); (iii) blinding of participants and personnel (performance bias); (iv) incomplete outcome data (attrition bias); (v) selective reporting

(reporting bias); and (vi) other bias, such as ethical aspects of study procedures.

Outcome Measures

Not all outcome data in intent-to-treat populations were available among all selected studies; hence, we extracted data in microbiologically modified intention-to-treat populations (mMITT) and modified intent-to-treat (MITT) [19] populations or clinically evaluable (CE) populations, as defined in individual studies. Target outcomes of interest in the searched studies were clinical response (CR), microbiological response (MR), and a composite of clinical cure and microbiological eradication (CC) at the test of cure (TOC) visit in the relevant populations for an efficacy measure; adverse events (AEs) and serious adverse events (SAEs) among the safety population during the treatment period were used for safety measures.

Statistical Analysis

We calculated treatment effects as risk ratios (RRs) and 95% CIs for dichotomous data with the DerSimonian-Laird random-effects model (REM) [20]. For the outcomes of treatment efficacy (CR, MR, and CC), RRs <1 favor new antibiotic treatment, whereas RRs <1 favor carbapenems for AEs and SAEs. Between-study heterogeneity was assessed using the χ^2 test ($P < .05$ as an indication of significant heterogeneity) and I^2 (>30% of I^2 was considered presence of heterogeneity).

To investigate the impact of outlying individual studies on the pooled effect estimate, sensitivity analyses were performed by excluding 1 trial each time and recalculating the pooled effect estimates. Publication bias was assessed using funnel plots with visual inspections. As the number of studies included was small, Egger's regression was applied to test the presence of bias. All statistical analyses were performed with Stata, version 15 (StataCorp, College Station, TX, USA).

RESULTS

The flow diagram in Figure 1 shows the process used to select studies. In total, 31 articles were identified by database searches, of which 13 were retrieved for full-text reading. Given that the focus of this meta-analysis was new antibiotic treatments vs carbapenem treatments, such as biapenem, doripenem, ertapenem, imipenem, meropenem, or panipenem, 5 articles were excluded due to being outside the scope of new antibiotics. Another 3 articles were removed because 1 trial included carbapenem treatments in both arms, 1 study was a duplication of an already selected article, and 1 report was a separate analysis from an original RCT published previously [21]. Finally, 5 articles met the inclusion criteria [22–25]. An additional registered trial was identified that is yet to be published in a peer-reviewed journal but with results available in the public domain, so it was also included in the analysis [26].

Study Characteristics

A total of 6 RCTs with 3343 subjects were analyzed in this study. Table 1 summarizes the main characteristics of the selected studies. All studies were multicentered, multinational randomized controlled trials funded by pharmaceutical companies. All participants included in this meta-analysis were ≥18 years old with cUTI, including acute pyelonephritis. One trial included patients with complicated intra-abdominal infections, yet relevant outcomes were stratified and presented separately from cUTI patients [23]. The same study compared ceftazidime-avibactam and the best available therapies, of which 97% were carbapenems [23]. Another 2 trials also tested ceftazidime-avibactam [22, 27]; the other trials used cefiderocol, plazomicin, and eravacycline, respectively [24–26]. For carbapenem treatments, 2 studies used imipenem-cilastatin, while the remaining trials employed doripenem, meropenem, or ertapenem, respectively [22–25, 27]. The primary end point of all trials was measured at the "test of cure" (TOC) visit, variably measured from initial treatment to 5 to 10 days after the last study drug treatment. This ranged from 12 to 31 days after randomization. The dosage, delivery method, and duration of each treatment are shown in Table 1.

Risk of Bias Assessment in Selected Studies

The Cochrane risk of bias assessment tool was used to assess the quality of selected studies (Figure 2). All studies demonstrated sufficient random sequence generation and allocation concealment, thus low risk of selection bias. One trial used open-label antibiotics [23], and therefore performance bias and detection bias were rated with high risk. The remaining 4 trials were performed with a double-blind model, and hence they had a low risk for performance bias and detection bias [22, 24, 25, 27]. One study had a high risk of attrition and reporting bias because it had a significant number of dropouts and the outcomes were reported with subpopulations [22]. The other studies were rated as having unclear risk due to exclusion of participants after randomization [23–25, 27]. Detailed risk of bias assessments are presented in Supplementary Table 2.

Efficacy of Treatments

Efficacy of treatment in the selected studies was evaluated with clinical response rate, per-patient microbiological response rate, and composite cure at TOC in the relevant population groups. Five studies had the complete data of composite cure in an mMITT or MITT population at TOC, including 1631 participants in total [22, 24, 25, 27]. Pooled effect estimates suggested that the new antibiotic groups had a higher composite cure rate than the carbapenem groups (RR, 0.91; 95% CI, 0.79–1.04; $P = .15$) (Figure 3A) [22, 24, 25, 27]. However, the statistical evidence was weak, and significant heterogeneity was observed ($I^2 = 81.1\%$).

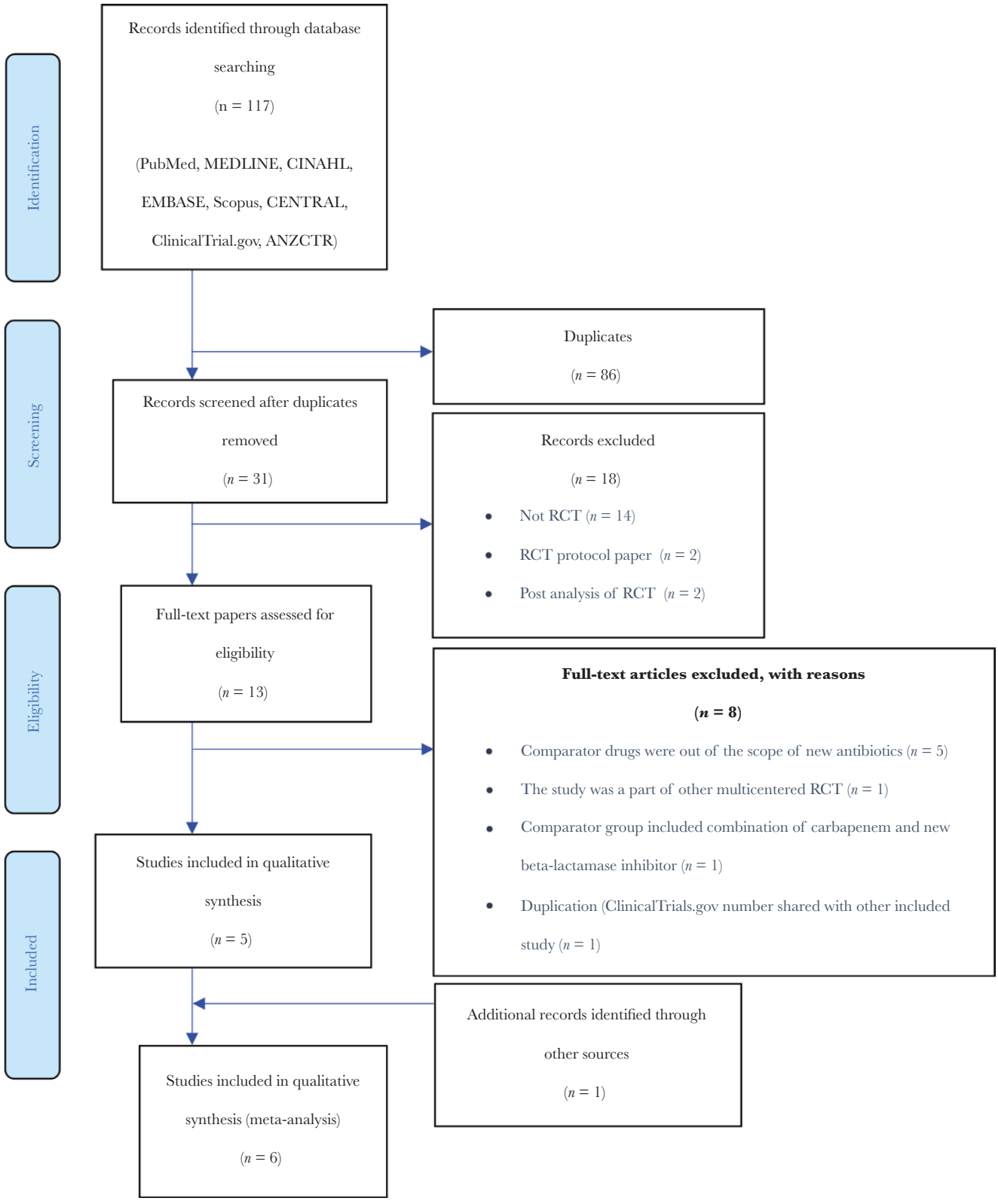

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram of assessed and included studies. Abbreviation: RCT, randomized controlled trial.

Table 1. Characteristics of Included RCTs

Author/Year	Study Design, Period	No. (RP[a]/SP[b])	Study Population	Population Characteristics		Drug Regimen		Oral Treatment	Duration of IV, d	Outcomes	Baseline Uropathogen	Subgroup Populations	End Point (TOC[c])
				Mean Age, y	Gender (F vs M), %	Carbapenem	New Antibiotics						
Vazquez, 2012 [21] NCT00690378	MC, MI, DB, RCT, June 2008–May 2018	137/135	Ages 18–90 cUTI or APN	48.2 ± 18.4/ 46.4 ± 18.2	73.1 vs 26.9/75.0 vs 25.0	Imipenem-cilastatin: 500 mg IV[d] 30-min infusion every 6 h	Ceftazidime-avibactam (ceftazidime: 500 mg plus avibactam: 125 mg) IV 30-min infusion every 8 h	Ciprofloxacin 500 mg or alternative oral therapy	6/5	CR,[e] MR,[f] CC,[g] AEs	*E. coli, P. aeruginosa, C. koseri, E. cloacae, P. mirabilis*	CE, ME, MITT	12–23
Carmeli, 2016 [22] NCT01644643	MC, MI, OL, RCT, Jan 2013–Aug 2014	306/305	Ages 18–90 with cUTI or (cIAI: stratified)	61.3 ± 15.3/ 64.3 ± 14.6	46.0 vs 54.0/44.4 vs 55.6	BAT[h] (97% carbapenem)[i]	Ceftazidime-avibactam (ceftazidime: 2 g plus avibactam: 500 mg) IV 2-h infusion every 8 h[j]		10/10	CR, MR, AEs	*Enterobactaeiaceae, E. coli, K. pneumoniae, E. cloacae, P. aeruginosa*	mMITT	12–31
Wagenlehner, 2016 [23] NCT01595438; NCT01599806	MC, MI, DB, RCT, Oct 2012–Aug 2014	1033/1020	Ages 18–90 with cUTI or APN	53.3 ± 18.6/ 51.4 ± 20.2	70.1 vs 29.9/68.3 vs 31.7	Doripenem: 500 mg IV every 8 h	Ceftazidime-avibactam (ceftazidime: 2 g plus avibactam: 500 mg) IV every 8 h	Ciprofloxacin (500 mg every 12 h) or sulfamethoxazole-trimethoprim (800 mg/160 mg every 12 h)	8/7	CR, MR, CC, AEs	*Enterobacteriaceae, E. coli, K. pneumoniae, P. mirabilis, E. cloacae,* EBSL-positive *Enterobacteriaceae, P. aeruginosa*	mMITT	21–25
Portsmouth, 2018 [24] NCT02321800	MC, MI, DB, RCT, Feb 2015–Aug 2016	452/448	Patients aged ≥18 y with cUTI or PN	61.3 ± 18.48/ 62.3 ± 16.1	60 vs 40/53 vs 47	Imipenem-cilastatin: 1 g IV every 8 h (doses of 3 g per day were permitted for those with *P. aeruginosa* infection)	Cefiderocol: 2 g IV every 8 h		9/9	CR, MR, CC, AEs	*E. coli, K. pneumoniae, P. aeruginosa, P. mirabilis, Enterobacter cloacae* complex, others	mMITT	14–23
Wagenlehner, 2019 [25] NCT02486627	MC, MI, DB, RCT, Jan–Sep 2016	609/604	Patients aged ≥18 y with cUTI/APN	60.0 ± 17.9/ 58.8 ± 18.0	49.2 vs 50.8/55.9 vs 44.1	Meropenem: 1 g IV every 8 h	Plazomicin: 15 mg per kg		9.2/8.9	CR, MR, CC, AEs	*Enterobacteriaceae, E. coli, K. pneumoniae, P. mirabilis, E. cloacae*	mMITT	15–19
IGNITE 3, NCT03032510	MC, MI, DB, RCT, Jan 2017–Apr 2018	1205 participants (randomized 1:1)				Ertapenem: 1 g every 24 h	Eravacycline: 1.5 mg/kg every 24 h		Not provided	CC	Not provided	mMITT	14–17

Abbreviations: AE, adverse event; APN, acute pyelonephritis; CC, clinical cure; CE, clinically evaluable; cIAI, complicated intra-abdominal infection; CR, clinical response; cUTI, complicated urinary tract infection; DB, double-blind; IV, intravenous; MC, multicenter; MI, multi-international; MITT, modified intention-to-treat population; mMITT, microbiologically modified intention-to-treat population; MR, microbiological response; PN, pyelonephritis; RCT, randomized controlled trial; TOC, test of cure.

[a]Randomized population (all patients who were randomly allocated to treatment groups).

[b]Safety population (all patients who received at least 1 dose of IV).

[c]Treatment of cure visit: in ME population (population characteristics: carbapenem group vs new antibiotic group); mean age ± SD.

[d]Intravenous; duration of IV: median days of IV treatment (carbapenem group vs new antibiotics group).

[e]Clinical response (clinical cure, complete resolution of clinical signs and symptoms of cUTI).

[f]Microbiological response (microbiological eradication, reduction of the urine pathogen to $<10^4$ colony-forming units/mL).

[g]Composite cure (favorable microbiological and clinical response).

[h]Best available therapy [22].

[i]Doripenem (11), ertapenem (1), imipenem; 1.5–4.0 g (76), meropenem; 1.5–3.0 g (57), colistin + imipenem (1).

[j]Dose modification for patients with renal impairment was applied.

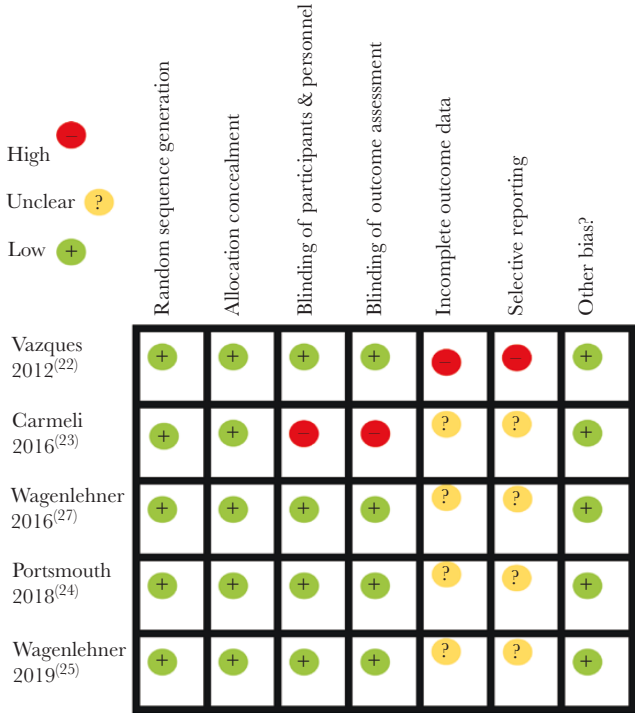

Figure 2. Risk of bias summary. Ratings were based on the Cochrane guideline. Red circles, green circles, and yellow circles indicated high risk, low risk, and unclear risk, respectively.

For clinical response, 5 RCTs (including 1914 participants) reported that there was no significant difference between carbapenem and the new antibiotic treatment in clinical response at TOC visit (RR, 1.00; 95% CI, 0.98–1.04; $P = .83$) (Figure 3B) [22–25, 27].

Regarding microbiological response, 5 studies (with 1945 participants) reported the per-patient microbiological eradication rate in an ME population or mMITT population at TOC [22–25, 27]. The pooled effect estimates showed that new antibiotics had greater rates of microbiological eradication than carbapenems (RR, 0.85; 95% CI, 0.79–0.91; $P < .01$) with moderate heterogeneity ($I^2 = 33.7\%$) (Figure 3C). Nevertheless, the 95% CI suggests that the proportion of heterogeneity can fall between 0% and 75%, and therefore, the heterogeneity in the true effect size remains unclear.

Safety of Treatments

Adverse events and serious adverse events were reported in all published papers, including 2512 patients [22–25, 27]. Two studies reported "any adverse events" and drug-related adverse events separately. The rates of AEs and SAEs were not significantly different between treatment groups (RR_{AEs}, 1.09; 95% CI, 0.93–1.29; $P = .297$; $I^2 = 59.1\%$; and RR_{SAEs}, 0.96; 95% CI, 0.53–1.76; $P = .896$; $I^2 = 44.1\%$, respectively) (Figure 4A and B). The total number of patients who discontinued treatment due to AEs was 20 in the new antibiotic arms and 17 in the carbapenem arms. In total, 8 deaths were observed in 5 studies (4 deaths in each arm); however, the association of death with antibiotic treatment was not specified.

Sensitivity Analyses

We performed sensitivity analyses to assess the influence of each selected study on the pooled effect estimates. For composite cure, heterogeneity was eliminated by excluding the IGNITE-3 trial (eravacycline vs ertapenem) with increment in favor of new antibiotic treatments (RR, 0.86; 95% CI, 0.81–0.93; $P < .01$; $I^2 = 7.8\%$) (Supplementary Table 5). Also, the sensitivity analysis revealed that the doripenem vs ceftazidime/avibactam trial was the strongest contributor to heterogeneity for the outcomes of MR, AEs, and SAEs (Supplementary Tables 3–5) [22, 24, 25, 27]. Interestingly, heterogeneity in CR was not detected, yet the 95% CIs were too wide to confirm significance. In the subgroup analysis including only ceftazidime-avibactam treatment, no differences were reported regarding CC, CR, and MR.

Publication Bias

With the small number of included studies, evaluation of the presence of publication bias was difficult. Visual inspection of funnel plots in each CC, CR, and MR suggests different spread trends in each outcome (Figure 5). When asymmetries (bias) were tested using Egger's metaregression test, all P values were large, suggesting statistically nonsignificant asymmetry (Supplementary Table 6).

DISCUSSION

This meta-analysis compared the efficacy and safety of new antibiotic treatments and carbapenem treatments for patients with cUTIs in 6 RCTs, with all included trials designed as noninferiority trials, following FDA guidelines [22–27]. We identified no significant difference between the new treatments examined and the carbapenem comparator for the composite measure of clinical and microbiological cure, though a favorable trend toward the new treatments was observed (RR, 0.91; 95% CI, 0.79–1.04). When clinical response and microbiological cure were investigated separately, there were no differences in clinical response between new antibiotic treatments and carbapenem treatments. However, microbiological eradication rates were significantly higher in the new antibiotic treatments group compared with the carbapenem treatment groups (RR, 0.85; 95% CI, 0.79–0.91). There were no differences in the occurrence of AEs and SAEs between treatment arms.

The reasons for lower microbiologic eradication rates when carbapenems were used need further exploration. Carbapenem resistance is not the explanation, as overt carbapenem resistance was not found in the infecting isolates in these studies. There remains the possibility of "hidden" carbapenem resistance due to comparatively weak carbapenemases such as OXA-48 and related enzymes. Delivery of drug to the site of infection

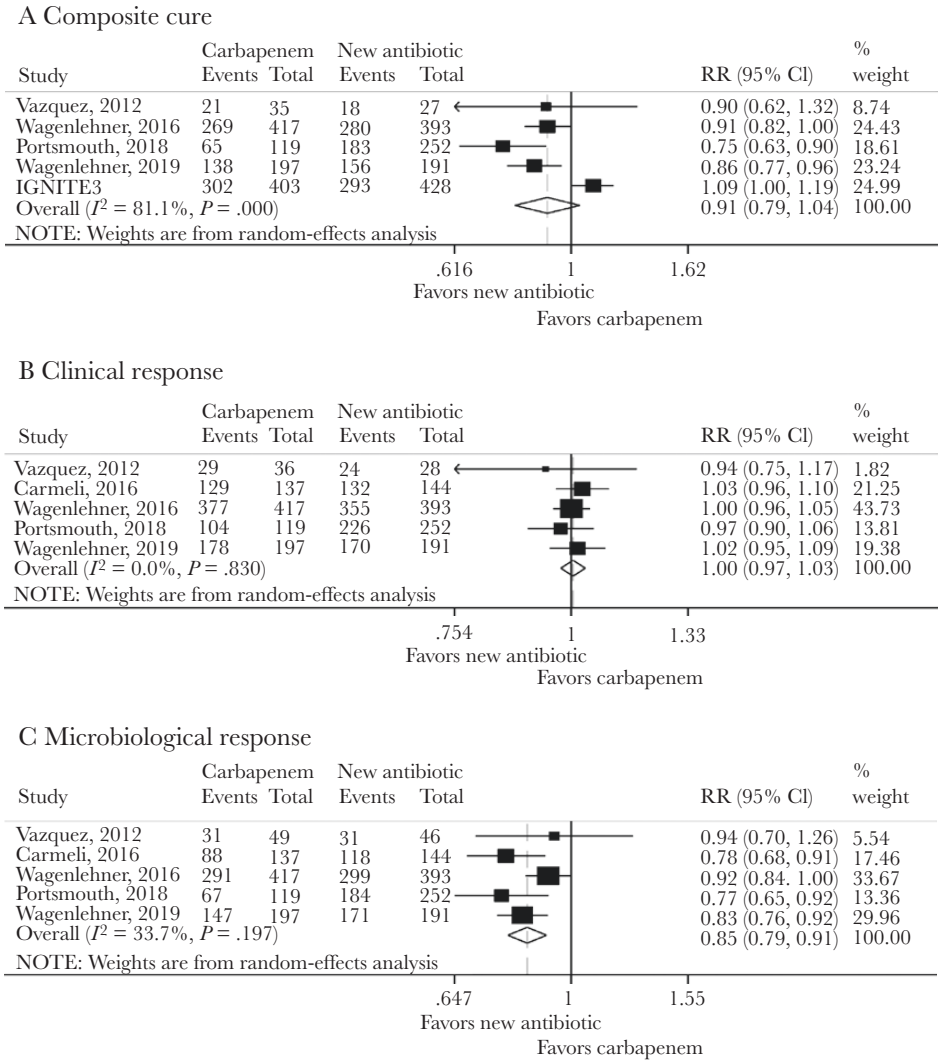

Figure 3. Forest plot of the meta-analysis for effects of new antibiotic treatments vs carbapenem treatments for patients with complicated urinary tract infection at test of cure visit: (A) composite cure in the microbiologically modified intent-to-treat population (mMITT) or modified intent-to-treat population (MITT); (B) clinical response in the mMITT or clinically evaluable population; (C) microbiological response in the MITT or mMITT population. I^2 shows proportion of inconsistency. Abbreviation: RR, risk ratio.

seems unlikely to be an explanation, as carbapenems manifest high urine concentrations due to good renal clearance.

There are several potential pathogenic mechanisms for explaining recurrent urinary tract colonization: (1) bacterial biofilms on the surface of a foreign body (eg, urinary catheter, stent, or calculi), (2) intracellular bacterial biofilms in superficial bladder cells [28], (3) re-infection from intestinal microbiota [29], and (4) external re-infection [30].

How could carbapenems fail to prevent recurrent urinary tract colonization? One possibility is that carbapenems do not penetrate biofilms associated with indwelling urinary catheters or urinary tract stents or calculi or that carbapenems trigger the formation of intracellular biofilms; however, there is no evidence that comparators have a higher efficacy against bacterial biofilms or lower bacterial biofilm induction. A more comprehensive explanation could be the fact that carbapenems have potent activity against the anaerobe components of the vaginal microbiota, in contrast to the comparators included in this meta-analysis (cefiderocol, plazomicin, ceftazidime-avibactam), which have poor or no activity against anaerobes. This is important, as in adult monkeys it has been documented that the delivery of amoxicillin into the vagina significantly reduces colonization resistance to *E. coli* from the intestinal microbiota, favoring its spread to the urethra and finally causing UTI. In contrast, trimethoprim and nitrofurantoin did not reduce colonization resistance [31]. In line with this evidence, Hooton et al. [32] performed a randomized study in females with UTI assigned to receive amoxicillin-clavulanate or ciprofloxacin (with no anaerobic activity) for 3 days. After 2 weeks of follow-up, clinical success was significantly higher in the ciprofloxacin arm (76% vs 95%; $P < .001$) while vaginal colonization with *E. coli* was significantly higher in the amoxicillin-clavulanate arm

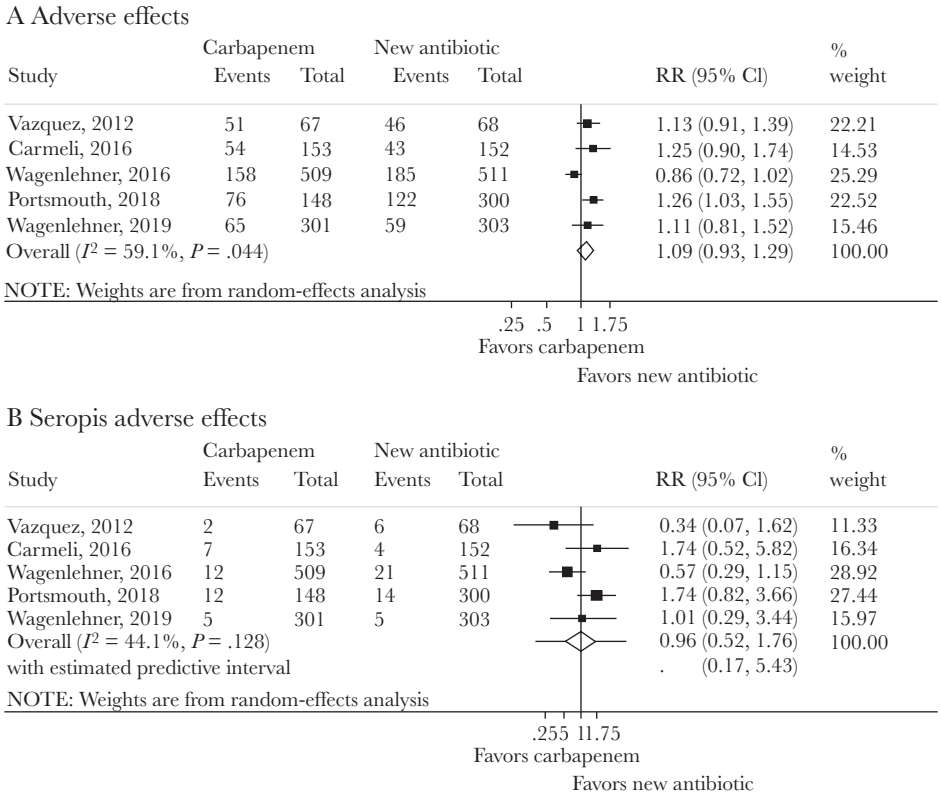

Figure 4. Forest plot of the meta-analysis for safety outcome of new antibiotic treatments vs carbapenem treatments for patients with complicated urinary tract infections: (A) adverse events in the safety population; (B) serious adverse events in the safety population. I^2 shows proportion of inconsistency. Abbreviation: RR, risk ratio.

(45% vs 10%; $P < .001$). These studies support the importance of maintaining the vaginal microbiota to avoid the re-colonization of the urinary tract.

We hypothesize that what happens with carbapenems is not a failure in bacterial eradication but a reduction in the colonization resistance of the vaginal microbiota by rectal *Enterobacterales*. Interestingly, a recent trial comparing meropenem-vaborbactam with piperacillin-tazobactam in cUTI demonstrated that both antibiotics had comparable microbiological eradication rates at the test of cure visit [33]. Both rates are similar to those reported in the present meta-analysis for the carbapenem arm, suggesting that antibiotics with broad-spectrum and anaerobic activity are associated with a more potent vaginal dysbiosis. The prevalence of women in these clinical trials ranged between 45 and 75%; therefore, the difference between carbapenems and comparators (without anaerobic activity) may be even higher when analyzing only the results in women. On the other hand, the impact of peri-urethral dysbiosis in microbiologic eradication in men with UTIs is not well studied, so we cannot rule out a potentially deleterious effect of carbapenems in men too. As orally administered carbapenems are likely to be future candidates for cUTI trials and intravenous carbapenems are likely to be frequently used as comparator agents for new beta-lactam/beta-lactamase inhibitor combinations, further work needs to be done as to why carbapenems have lower microbiologic eradication rates than new antibiotics.

Several limitations to our meta-analysis should be considered. The IGNITE3 study was not included in the risk of bias assessment because limited information was available to justify each item. One of the included studies was rated as high risk for attrition bias and reporting bias, while biases associated with other included studies were identified due to uneven numbers of dropouts between treatment groups, additional oral antibiotic use in 2 included studies (and the weak statistical power of each of these trials), and analysis using CE, MITT, and mMITT populations instead of a conventional intention-to-treat (ITT) population [22]. These factors may have introduced bias to the true pooled estimate of each outcome. However, sensitivity analyses showed that there were no significant changes in the pooled estimates. In 1 study, although 97% of regimen drugs were carbapenems, we could not separate the outcome data of carbapenem treatments from those of other treatments among a "best available therapy" (BAT) group [23]. This may have increased or reduced the pooled effect estimates; however, impacts are assumed to be small, because only 5 patients were treated with drugs other than carbapenems among 137 subjects. It is noteworthy that the timing of the TOC visit was variable between studies, and it remains possible that this may have had

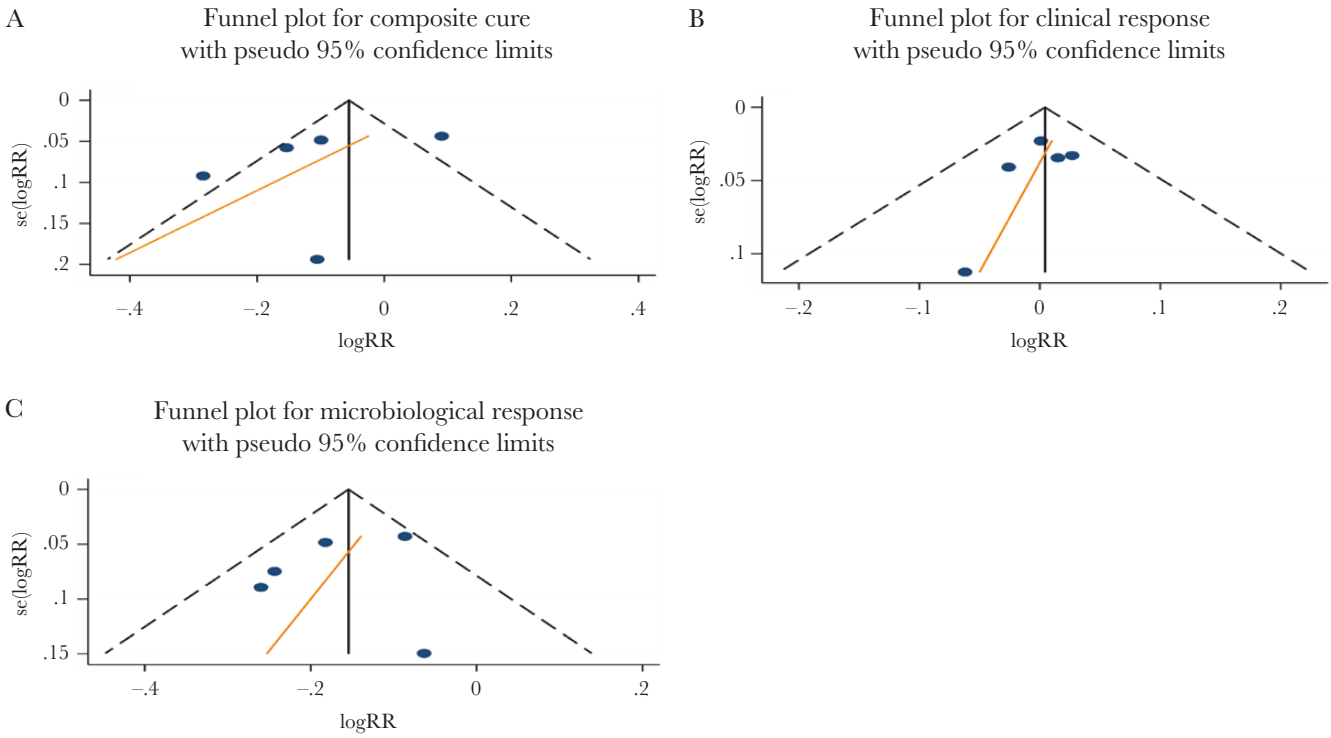

Figure 5. Meta-funnel plots comparing carbapenem and new antibiotics for each outcome: (a) composite cure, (b) clinical response, (c) microbiological response. The vertical line corresponds to the summary log(RR) as estimated from the random effects model. Red regression lines with SE regression on effect size are embedded. Abbreviation: RR, risk ratio.

an impact on microbiologic response. Additionally, the use of oral antibiotics in 2 studies following the IV course is also potentially important—in the 2 studies in which oral antibiotics were permitted, there was minimal difference in microbiological response.

Of note, these studies did not require multidrug-resistant pathogens for enrollment; as such, the generalizability of our findings in this clinical setting is unclear. Further trials in settings with higher levels of antimicrobial resistance are warranted. There was significant observed heterogeneity between the studies in terms of population characteristics; dose, duration, and nature (monotherapy or combination therapy) of treatments; and timing of end point assessment. Although these factors should be accounted for in the random-effects model, this variability needs to be acknowledged.

The evaluated articles considered microbiological failure based on the result of a urine culture at the TOC visit, but a genomic analysis was not performed in order to clarify if the isolated microorganism was the same as the 1 isolated in the index infection. In addition, whether microbiological eradication was associated with a lower risk of a subsequent episode of UTI was not evaluated, as the patients were no longer followed up beyond the TOC visit. Of 3 studies that reported recurrence rates of infections, 2 studies reported that incidence rates of microbiologic recurrence were lower in the new antibiotics group than the carbapenem group at late follow-up (5% vs 10% and 3.5% vs 8.1%) [24, 25], whereas 1 study found no differences between study arms (30.8% vs 33.3%) [22].

CONCLUSIONS

In conclusion, this meta-analysis indicates that new antibiotics can perform with similar clinical efficacy and safety but may have a better microbiological response compared with carbapenems for the treatment of patients with cUTIs. This result is consistent with the previous meta-analysis evaluating the efficacy and safety of ceftazidime-avibactam treatments compared with alternative antibiotic agents including carbapenems [14, 16, 34]. Our analysis included newly developed antibiotics, such as cefiderocol, plazomicin, and eravacycline, and may provide updated insights into cUTI treatment. In settings where there is a risk of a carbapenem-resistant pathogens, these new antibiotics could be an important therapeutic option [3]. Nevertheless, many questions still remain with regards to the appropriate use of new antibiotics, as resistance to newer agents may emerge quickly without cautious use [35]. It is important to acknowledge that there might be variability in the regulatory and clinical definitions of cUTI. As it is likely that carbapenems will be a comparator for upcoming registrational trials of other new antibiotics for cUTI, the mechanisms by which microbiologic

response rates are inferior when carbapenems are used need to be further explored.

Supplementary Data

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

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References

1. Likis F. Urinary tract infections. J Midwifery Womens Health **2017**; 62:241–2.
2. Nicolle LE. Urinary tract infection. Crit Care Clin **2013**; 29:699–715.
3. Gandhi T, Flanders SA, Markovitz E, et al. Importance of urinary tract infection to antibiotic use among hospitalized patients. Infect Control Hosp Epidemiol **2009**; 30:193–5.
4. Eichenberger EM, Thaden JT. Epidemiology and mechanisms of resistance of extensively drug resistant gram-negative bacteria. Antibiotics (Basel) **2019**; 8:37. doi:10.3390/antibiotics8020037.
5. Mayor S. First WHO antimicrobial surveillance data reveal high levels of resistance globally. BMJ **2018**; 360:k462.
6. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol **2015**; 13:269–84.
7. Tabak YP, Sung AH, Ye G, et al. Attributable clinical and economic burden of carbapenem-non-susceptible gram-negative infections in patients hospitalized with complicated urinary tract infections. J Hosp Infect **2019**; 102:37–44.
8. Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. Carbapenems: past, present, and future. Antimicrob Agents Chemother **2011**; 55:4943–60.
9. Harris PNA, Tambyah PA, Lye DC, et al; MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA **2018**; 320:984–94.
10. Harting J. Carbapenem-resistant Enterobacteriaceae infections: a review of epidemiology and treatment options. Univ. Loisville J. Respir. Infect. **2019**; 3. doi:10.18297/jri/vol3/iss1/4.
11. World Health Organization. Investigating in the development of new antibiotics and their conservation—setting up a global antibiotic research and development partnership. Available at: https://www.who.int/phi/implementation/consultation_imnadp/en/. Accessed 17 March 2020.
12. Medina E, Pieper DH. Tackling threats and future problems of multidrug-resistant bacteria. How to Overcome the Antibiotic Crisis. Curr Top Microbiol Immunol **2016**; 398:3–33.
13. Bassetti M, Righi E, Carnelutti A. Light and shade of antibiotics recently approved and in advanced development for critically ill patients. In: Vincent J-L, ed. Annual Update in Intensive Care and Emergency Medicine 2019. Brussels, Belgium: Springer International Publishing; **2019**:447–98.
14. Chen M, Zhang M, Huang P, et al. Novel β-lactam/β-lactamase inhibitors versus alternative antibiotics for the treatment of complicated intra-abdominal infection and complicated urinary tract infection: a meta-analysis of randomized controlled trials. Expert Rev Anti Infect Ther **2018**; 16:111–20.
15. Singh KP, Li G, Mitrani-Gold FS, et al. Systematic review and meta-analysis of antimicrobial treatment effect estimation in complicated urinary tract infection. Antimicrob Agents Chemother **2013**; 57:5284–90.
16. Zhong H, Zhao XY, Zhang ZL, et al. Evaluation of the efficacy and safety of ceftazidime/avibactam in the treatment of gram-negative bacterial infections: a systematic review and meta-analysis. Int J Antimicrob Agents **2018**; 52:443–50.
17. Moher D, Liberati A, Tetzlaff J, et al; for the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. Ann Intern Med **2009**; 151:264–9, W64.
18. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ **2011**; 343:d5928.
19. de With K, Allerberger F, Amann S, et al. Strategies to enhance rational use of antibiotics in hospital: a guideline by the German Society for Infectious Diseases. Infection **2016**; 44:395–439.
20. Serghiou S, Goodman SN. Random-effects meta-analysis: summarizing evidence with caveats. JAMA **2019**; 321:301–2.
21. Park DW, Peck KR, Chung MH, et al. Comparison of ertapenem and ceftriaxone therapy for acute pyelonephritis and other complicated urinary tract infections in Korean adults: a randomized, double-blind, multicenter trial. J Korean Med Sci **2012**; 27:476–83.
22. Vazquez JA, González Patzán LD, Stricklin D, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. Curr Med Res Opin **2012**; 28:1921–31.
23. Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis **2016**; 16:661–73.
24. Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. Lancet Infect Dis **2018**; 18:1319–28.
25. Wagenlehner FME, Cloutier DJ, Komirenko AS, et al; EPIC Study Group. Once-daily plazomicin for complicated urinary tract infections. N Engl J Med **2019**; 380:729–40.
26. Tetraphase Pharmaceuticals Inc. Tetraphase announces top-line results from IGNITE3 phase 3 clinical trial of eravacycline in complicated urinary tract infections (CUTI). Available at: https://ir.tphase.com/news-releases/news-release-details/tetraphase-announces-top-line-results-ignite3-phase-3-clinical. Accessed 25 May.
27. Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. Clin Infect Dis **2016**; 63:754–62.
28. Anderson GG, Palermo JJ, Schilling JD, et al. Intracellular bacterial biofilm-like pods in urinary tract infections. Science **2003**; 301:105–7.
29. Yamamoto A, Naruo S, Kagawa S, et al. Long-term follow-up of the Le Duc-Camey antireflux technique [in Japanese]. Nihon Hinyokika Gakkai Zasshi **1997**; 88:414–9.
30. Thanert R, Reske KA, Hink T, et al. Comparative genomics of antibiotic-resistant uropathogens implicates three routes for recurrence of urinary tract infections. mBio **2019**; 10:e01977-19.
31. Winberg J, Herthelius-Elman M, Möllby R, Nord CE. Pathogenesis of urinary tract infection–experimental studies of vaginal resistance to colonization. Pediatr Nephrol **1993**; 7:509–14.
32. Hooton TM, Scholes D, Gupta K, et al. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. JAMA **2005**; 293:949–55.
33. Kaye KS, Bhowmick T, Metallidis S, et al. Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial. JAMA **2018**; 319:788–99.
34. Sternbach N, Leibovici Weissman Y, Avni T, Yahav D. Efficacy and safety of ceftazidime/avibactam: a systematic review and meta-analysis. J Antimicrob Chemother **2018**; 73:2021–9.
35. Larsson DGJ, Andremont A, Bengtsson-Palme J, et al. Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance. Environ Int **2018**; 117:132–8.