Systematic Review and Meta-Analysis

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Carbapenems vs alternative antibiotics for the treatment of complicated urinary tract infection

A systematic review and network meta-analysis

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Abstract

Background: Complicated urinary tract infections (cUTI) are universal reasons for hospitalization, and highly likely to develop into sepsis or septic shock. Carbapenem antibiotics with potentially higher efficacy or with fewer and milder side effects have increased in popularity, but evidence is limited by a scarcity of randomized controlled trials (RCTs) comparing different carbapenem antibiotics for cUTI. Network meta-analysis is a useful tool to compare multiple treatments when there is limited or no direct evidence available.

Objective: The aim of this study is to compare the efficacy and safety of different carbapenems with alternative antibiotics for the treatment of cUTI.

Methods: Pubmed, Medline, CENTRAL, and Embase were searched in November 2018. Studies of cUTI patients receiving carbapenem were included. We performed network meta-analysis to estimate the risk ratio (RR) and 95% credible interval (CrI) from both direct and indirect evidence; traditional meta-analysis was also performed. Primary outcomes were clinical and microbiological treatment success.

Results: A total of 19 studies and 7380 patients were included in the analysis. Doripenem (DOPM) was associated with lower clinical treatment success rates than other carbapenems. Although the efficacy of other carbapenems by RRs with 95% CrIs did not show statistical differences, the cumulative rank probability indicated that meropenem/vaborbactam (MV), ertapenem (ETPM), and biapenem (BAPM) had higher clinical and microbiological treatment success rates; imipenem/cilastatin (IC) and MV showed higher risk of adverse events (AEs).

Conclusions: MV was associated with higher treatment success rates for cUTI, especially for cUTI caused by carbapenem-resistant uropathogens, but also with higher risk of AEs. Our findings suggest MV as a first-choice treatment of carbapenem-resistant cUTI. ETPM, BAPM, and meropenem (MEPM) is another reasonable choice for cUTI empiric therapy.

Abbreviations: AEs = adverse events, BAPM = biapenem, CA = ceftazidime/avibactam, CFPM = cefepime, CrI = credible interval, CTAX = ceftriaxone, cUTI = complicated urinary tract infection, DOPM = doripenem, ETPM = ertapenem, IC = imipenem/cilastatin, LEFC = levofloxacin, LFU = late follow-up, MEPM = meropenem, MV = meropenem/vaborbactam, PT = piperacillin/tazobactam, RB = relebactam, RCT = randomized controlled trial, RR = risk ratio, TOC = test-of-cure.

Keywords: antibacterial agents, carbapenem, complicated urinary tract infection, network meta-analysis, review literature as topic, systematic review

Editor: Duane R. Hospenthal.

XT and QP made an equal contribution.

This project was supported by the scientific research and technological development projects of Hechi, Guangxi Province of China [Heke B1824–4].

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

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How to cite this article: Tan X, Pan Q, Mo C, Li X, Liang X, Li Y, Lan Y, Chen L. Carbapenems vs alternative antibiotics for the treatment of complicated urinary tract infection: A systematic review and network meta-analysis. Medicine 2020;99:2(e18769).

Received: 24 June 2019 / Received in final form: 22 November 2019 / Accepted: 11 December 2019

http://dx.doi.org/10.1097/MD.0000000000018769

1. Introduction

Complicated urinary tract infections (cUTI) are universal reasons for hospital admission, with high likelihood of developing into septic shock or sepsis and these infections are a major cause of morbidity, mortality, and excess health care costs.[1–3] Appropriate and prompt administrations of antibiotics for treatment of cUTI can improve clinical outcomes and decrease mortality and healthcare costs.[1] Treatment guidance for urinary tract infections includes recommendations of therapy for targeted and empiric treatment of the major causative pathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, and non-*Enterobacteriaceae* organisms such as *Pseudomonas aeruginosa*.[1,4,5]

The empiric antimicrobial treatment of complicated infectious diseases thus requires targeting a broad spectrum of potential pathogens. Carbapenems are among the β-lactam antibiotics and have remarkable microbiological activity against the majority of Gram-negative bacteria. Carbapenem use is increasing worldwide; carbapenems have the broadest spectrum activity of all β-lactam antimicrobials and therefore are considered the drug of choice in severe, multidrug-resistant, and complicated infections.[6] However, long-term and increased application of carbapenem can lead to the development and spread of drug-resistant bacteria, and increased the relative risk of infection with drug-resistant Gram-negative bacteria.[7] In recent years, antimicrobial resistance has constituted a global burden and become a major threat to public health, and poses new challenges for better treatment.[8,9] Carbapenem-resistant *Enterobacteriaceae* worldwide are identified as an urgent threat to human health and life. The most frequent infections due to carbapenem-resistant *Enterobacteriaceae* occur in cUTI, including acute pyelonephritis, and are usually healthcare associated.[10] Mortality due to carbapenem-resistant *Enterobacteriaceae* infections ranges from 20% to 54.3%. Clearly, for better treatment options are needed.[11–14]

Recently, 2 novel carbapenem-β-lactamase inhibitor combinations: imipenem/cilastatin/relebactam (ICRB) and meropenem/vaborbactam (MV) have been used to combat these resistant Gram-negative pathogens and broaden the spectrum of imipenem/cilastatin (IC) and meropenem (MEPM), respectively, against β-lactamase-producing Gram-negative bacilli.[15,16]

Some randomized controlled trials (RCTs) have been published evaluating the efficacy and safety of different carbapenems for treating cUTI. However, physicians have little evidence upon which to base a selection from these first-choice carbapenem antibiotics.

Network meta-analysis has enabled the comparison of multiple treatment arms collectively by combining information from all randomized comparisons of 2 treatments and evidence from indirect comparisons based on a common comparator, and is currently a very active research topic. The main aim of the current study is to compare the effectiveness and safety of different carbapenems or carbapenem-β-lactamase inhibitor combinations vs alternative antibiotics for the treatment of cUTI. For this purpose, we assessed clinical treatment success and microbiological treatment success as the primary outcomes. Adverse events (AEs) was also assessed as the secondary outcome.

2. Methods

2.1. Search strategy and selection criteria

The study was approved by the ethics institutional review board of the People's Hospital of Hechi. PubMed, Embase, Medline (via Ovid SP), and Cochrane library databases up to November 2018 were systematically searched. The following search terms were used: "complicated urinary tract infection", "cUTI", "carbapenem", "imipenem", "meropenem", "biapenem", "ertapenem", "doripenem", "faropenem", "panipenem", "razupenem", "tebipenem", "tomopenem", and "sanfetrinem". No language restriction was imposed. We included articles regardless of the language of publication and conference abstracts. The reference lists of all retrieved articles were also reviewed to identify additional articles missed by using these search terms. The authors approved all enrolment studies.

2.2. Inclusion criteria

Studies meeting the following criteria were included:

(i) population: cUTI patients;
(ii) intervention: carbapenems for treatment of cUTI;
(iii) comparison: placebo or other antimicrobial agents;
(iv) outcome: primary outcomes: clinical treatment success and microbiological treatment success; secondary outcomes: AEs;
(v) design: RCTs.

2.3. Exclusion criteria

The exclusion criteria were

(i) not RCTs: reviews, meta-analysis, observational studies, case reports, editorials, nonclinical studies, and case observations;
(ii) reduplicated studies;
(iii) studies with incomplete data
(iv) improper outcome measures.

2.4. Selection of studies and data extraction

A comprehensive search of databases was performed by 2 researchers (Tan and Pan) who deleted duplicate records, screened the titles and abstracts for relevance, and identified each as excluded or requiring further assessment. We reviewed the full-text articles designated for inclusion and manually checked the references of the retrieved articles and previous reviews to identify additional eligible studies. Discrepancies were resolved by consensus. The following data were extracted from each study: study design, first author, and year of publication, number of patients, age category (adult or child), interventions, comparisons, and outcomes.

2.5. Risk of bias assessment

Three reviewers (Tan, Pan, and Mo) independently evaluated the methodological quality of identified studies. The "risk of bias tool" referred to the Cochrane Handbook for Systematic Reviews of Interventions version 5.3.0 was used to assess methodological quality.[17,18] In terms of the assessment criteria, each study was rated and assigned one of the 3 following risk of bias: low: if all quality criteria were adequately met, the study was deemed to have a low risk of bias; unclear: if one or more of the quality criteria was only partially met or was unclear, the study was deemed to have a moderate risk of bias; or high: if one or more of the criteria was not met, or not included, the study was deemed to have a high risk of bias.[19,20]

2.6. Data analysis

A pair-wise meta-analysis was performed to combine studies addressing the same outcome and carbapenem antibiotics. We

estimated a relative risk (RR), and 95% credible interval (CrI) to compare efficacy and safety of different carbapenems for each pair of available treatments. In the case of zero counts, a correction of 0.5 was added for all arms within the RCT. Heterogeneity was assessed by the I^2 test, with an $I^2 > 50\%$ considered as the existence of significant heterogeneity.

With non-existence of heterogeneity, a fixed-effect model was applied and RRs were calculated by the Mantel-Haenszel method. With the presence of heterogeneity, RRs were calculated by random-effect model and the DerSimonian and Laird method. Calculations in traditional meta-analyses were performed by Stata 14.0 software (Stata Corp, College Station, TX). Publication bias was examined by funnel plot. Funnel plots and network plots were also constructed by Stata software.[21]

Network meta-analysis concerning multiple treatments was performed by a random-effect model within a Bayesian framework, using package "gemtc" version 0.8–2 of R software (version 3.5.1). RRs with 95% CrI were calculated by Markov chain Monte Carlo methods.[22,23]

For each model, we set at least 200,000 simulations for each chain as the "burn-in" Markov chain Monte-Carlo simulations, yielding 200,000 iterations to obtain the RR of model parameters.[24,25] In addition, the pooled RRs from the network meta-analysis and RRs from pair-wise meta-analysis of direct comparisons were compared to estimate the consistency between direct and indirect comparisons. The node-splitting method was used to calculate the inconsistency of the model and assess the consistency. The method separated the evidence concerning certain comparisons into direct and indirect evidence, and the inconsistency was reported by its Bayesian P value.[26]

We also sorted the studied antimicrobial agents for each outcome based on their rank probabilities. The rank probabilities were calculated to obtain the hierarchy of each treatment. Based on the results of rank probabilities, physicians could make appropriate choices of carbapenem for treatment of cUTI.[27] The matrix of rank probabilities and the plot of rank probabilities were provided by the "gemtc" package simultaneously. From the direct plot of rank probabilities, we could easily find the ranking of each antimicrobial agent.[28] Finally, the bias of the magnitude of heterogeneity variance parameter I^2 was used to evaluate the global heterogeneity.

Sensitivity analyses were performed to assess the robustness of the findings. These used a fixed-effect model instead of a random-effect model. To determine whether the results were affected by study characteristics, we performed subgroup network meta-analysis on primary outcomes according to the result of time from treatment to test-of-cure (TOC) and late follow-up (LFU) visit.

3. Results

3.1. Study identification and selection

In total, 2632 records were retrieved from the initial database search. After removing 738 duplicate articles, 1894 records were eligible. Based on the inclusion and exclusion criteria, 1839 articles were excluded after a simple reading of the titles and abstracts of the articles. The remaining 55 full-text articles were assessed for eligibility. Then, studies were included if they met the criteria not a relevant study design, not RCT, meta-analysis, reported only combination, or no combination specifics. Finally, a total of 19 RCTs were included in the meta-analysis.[10,29–46] (Table 1). The selection process is shown in Fig. 1.

Table 1

Characteristics of included studies.

Study	Age category	Intervention		Comparison		Test of cure (d)	Late follow-up (d)	Blinding	n
		Carbapenems		Other antimicrobial agents					
Cannavino 2015[29]	C	DOPM 0.02 g/kg × 3		CFPM 50 mg/kg × 3		7–14	28–42	Double-blind	40
Chen 2014[30]	A	BAPM 0.3 g × 2	MEPM 0.5 g × 3					Signal-blind	144
Cox 1995[31]	A	MEPM 0.5 g × 3	IC 0.5 g × 3			5–20	≥21	None	235
Jia2010[32]	A	BAPM 0.3 g × 2	IC 0.5 g/0.5 g × 2			7–14		None	112
Jimenez-cruz 2002[33]	A	ETPM 1 g × 1		CTAX 1 g × 1		5–9	28–36	Double-blind	258
Kawada 1994[34]	A	BAPM 0.3 g × 2	IC 0.5 g/0.5 g × 2					Double-blind	219
Kawada 2000[35]	A	BAPM 0.3 g × 2	IC 0.5 g/0.5 g × 2					Double-blind	186
Kaye 2018[10]	A	MV 2 g/2 g × 3		PT 4 g/0.5 g × 3		17	21	Double-blind	550
Naber 2002[36]	A	IC 0.5 g/0.5 g × 3		PT 2 g/0.5 g × 3		5–9	28–42	Double-blind	337
Naber 2009[37]	A	DOPM 0.5 g × 3		LEFC 0.25 g × 2		5–11	28–42	Double-blind	753
Park 2012[38]	A	ETPM 1 g × 1		CTAX 2 g × 1		5–9		Double-blind	271
Redman 2010[39]	A	DOPM 0.5 g × 3		LEFC 0.25 g × 1		5–11	28–42	Double-blind	1179
Seo 2017[40]	A	ETPM 1 g × 1 or 0.5 g × 1		PT 4.5 g × 4 or 2.25 g × 4 or 8 g × 3	CFPM 2 g × 2 or 2 g × 1 or 1 g × 1			None	72
Sims 2017[41]	A	IC 0.5 g × 4 + RB 0.25 g or 0.125 g × 4	IC 0.5 g × 4			5–9	28–42	Double-blind	302
Tomera 2002[42]	A	ETPM 1 g × 1		CTAX 1 g × 1		5–9	28–42	Double-blind	592
Vazquez 2012[43]	A	IC 0.5 g × 4		CA 0.5 g/0.125 g × 3		12–13	28–42	Double-blind	135
Wagenlehner 2016[44]	A	DOPM 0.5 g × 3		CA 2 g/0.5 g × 3		21–25	42–52	Double-blind	1033
Wells 2004[45]	A	ETPM 1 g × 1		CTAX 1 g × 1		5–9	28–42	Double-blind	850
Yang 2007[46]	A	BAPM 0.3 g × 2	MEPM 0.5 g × 2			7–14		None	112

[Age category]: A = adult, C = child.

[Intervention and Comparison]: BAPM = biapenem, CA = ceftazidime/avibactam, CFPM = cefepime, CTAX = ceftriaxone, DOPM = doripenem, ETPM = ertapenem, IC = imipenem/cilastatin, LEFC = levofloxacin, MEPM = meropenem, MV = meropenem/vaborbactam, PT = piperacillin/tazobactam, RB = relebactam, n = number of patients randomized.

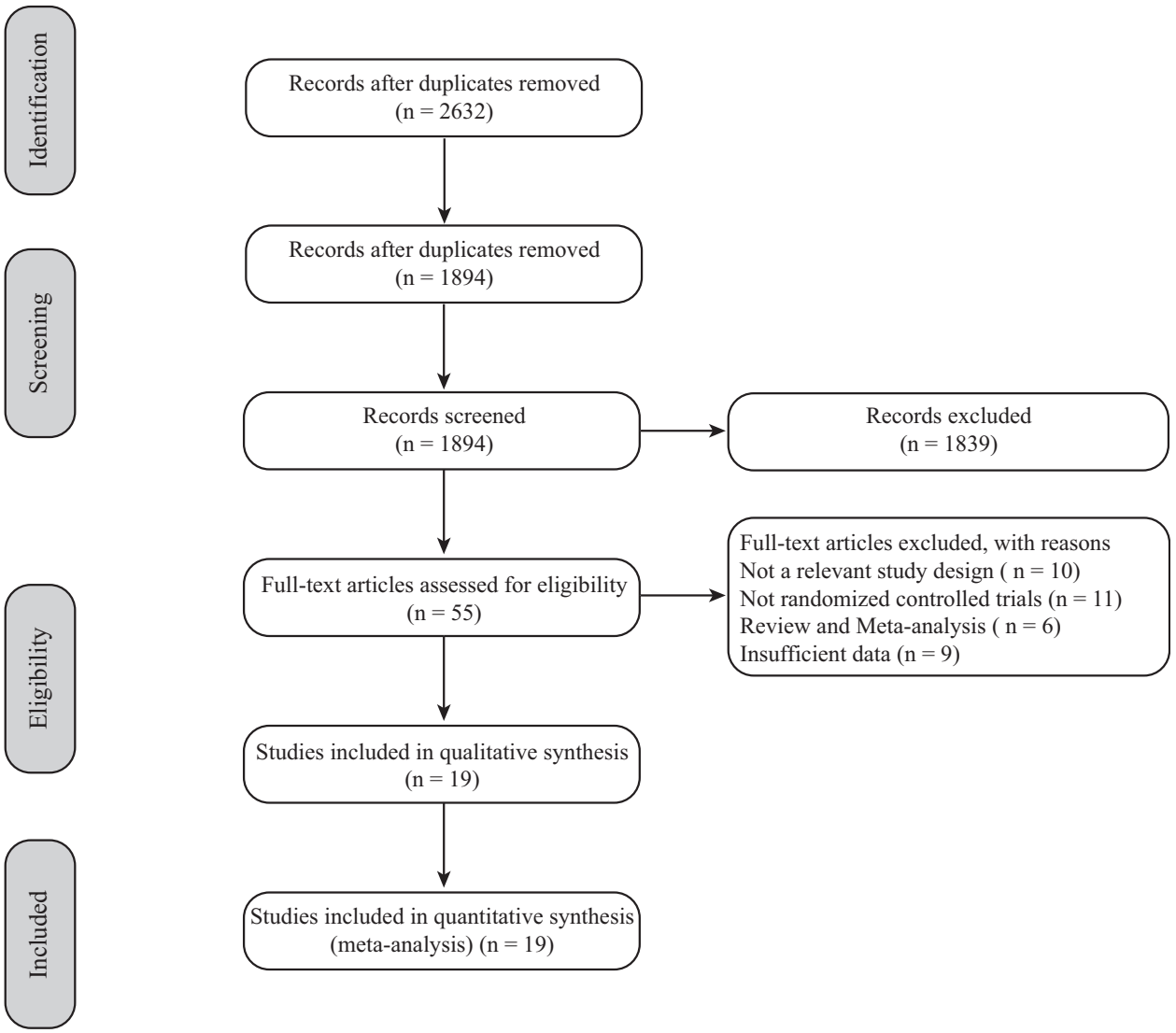

Figure 1. Selection process for the studies included in the meta-analysis.

3.2. Study characteristics

The basic characteristics of the included studies are listed in Table 1. Nineteen RCTs involving 7380 participants were included in the analysis. These studies were published from 1987 to 2017. The number of participants in the studies ranged from 40 to 1179. One study included only children and 18 included only adults. One study adopted a 3-arm design, and the other 18 used 2-arm trial designs.

The outcomes of risk of bias are summarized in Fig S1 (Supplemental Content Fig. S1, which illustrates the outcomes of the risk of bias of included studies, http://links.lww.com/MD/D586). The definitions of cUTI and definition of outcomes are shown in Table S1 (Supplemental Content Table S1, which illustrates the definition of clinical and microbiological outcomes, http://links.lww.com/MD/D596). Eight studies did not describe the randomization method. Fourteen studies adopted a double-blind design with low risk for performance bias and detection bias, and one study adopted a single-blind design. Four trials were performed in open-label model, with a high risk for performance bias and detection bias. As for attrition bias, two studies possessed high risk, with a relatively great amount of missing data, and the remaining 16 trials were assessed as low risk.

4. Results from network meta-analysis

4.1. Clinical treatment success

A total of 16 studies including 4287 patients provided data on clinical treatment success at end of treatment, direct or indirect between studied antimicrobial agents were compared with each other independently. The network plots of eligible comparisons for clinical treatment success are showed in Fig. 2(A) without heterogeneity or inconsistency. The funnel plots showed no asymmetry Fig S2 (Supplemental Content Fig. S2, which illustrates the funnel plot of clinical treatment success, http://links.lww.com/MD/D587).

Our results showed that, compared with doripenem (DOPM), biapenem (BAPM), ertapenem (ETPM), IC, ICRB, MEPM, MV, and piperacillin/tazobactam (PT) each appeared to have better

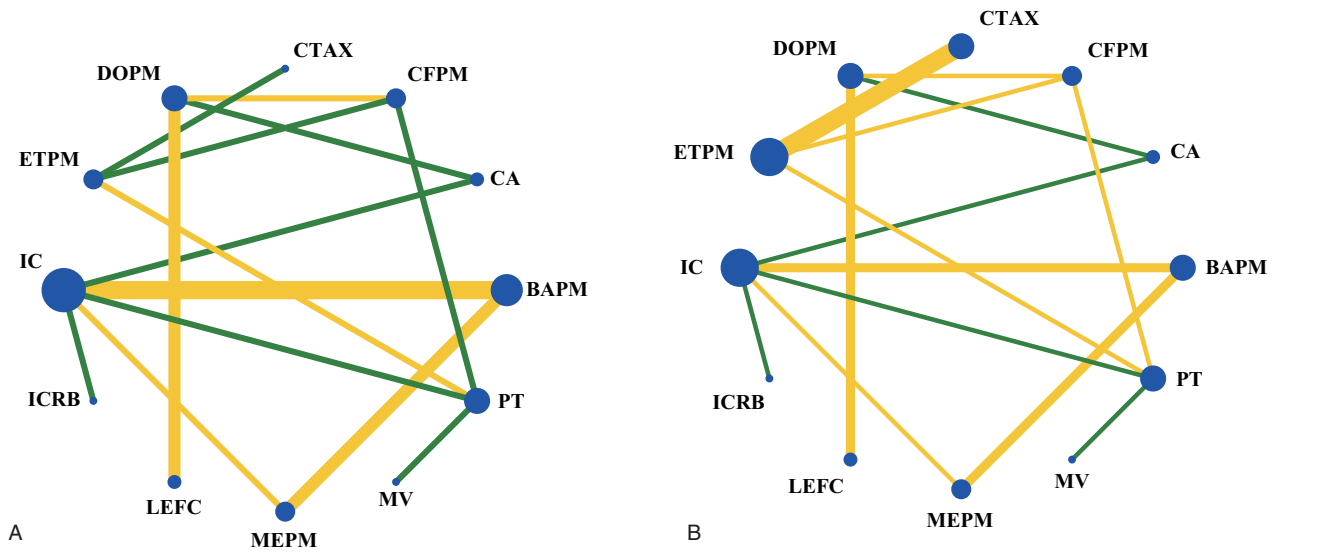

Figure 2. Network comparisons of studies included in the analyses. (A) clinical treatment success; (B) microbiological treatment success.

clinical treatment success (RR = 2.14, 95% CrI 1.07–7.82; RR = 2.14, 95% CrI 1.05–7.78; RR = 2.08, 95% CrI 1.05–7.58; RR = 2.07, 95% CrI 1.03–7.62; RR = 2.07, 95% CrI 1.04–7.56; RR = 2.17, 95% CrI 1.08–7.99; RR = 2.07, 95% CrI 1.04–7.54, respectively, Fig. 3 and Table 2). The effect of ETPM, IC, ICRB, MEPM, MV, and PT on clinical treatment success was similar to BAPM (RR = 1.00, 95% CrI 0.81–1.23; RR = 0.97, 95% CrI 0.90–1.06; RR = 0.97, 95% CrI 0.85–1.12; RR = 0.97, 95% CrI 0.89–1.05; RR = 1.01, 95% CrI 0.86–1.21; RR = 0.97, 95% CrI 0.85–1.11, respectively, Fig. 3 and Table 2). Furthermore, we found that the novel β-lactam/β-lactamase inhibitors combination ceftazidime/avibactam (CA) is similar to DOPM, cefepime (CFPM), and levofloxacin (LEFC) (RR = 1.02, 95% CrI 0.92–1.13; RR = 0.86, 95% CrI 0.43–1.39; RR = 0.95, 95% CrI 0.83–1.08), and appeared to have lower clinical treatment success compared to BAPM, ETPM, IC, ICRB, MEPM, MV, and PT (RR = 2.17, 95% CrI 1.09–7.97; RR = 2.17, 95% CrI 1.07–7.94; RR = 2.11, 95% CrI 1.07–7.73; RR = 2.10, 95% CrI 1.05–7.75; RR = 2.10, 95% CrI 1.06–7.71; RR = 2.21, 95% CrI 1.10–8.13; RR = 2.10, 95% CrI 1.06–7.67, respectively, Fig. 3 and Table 2).

The result from sensitivity analyses with studies using fixed-effect model analysis almost replicated the result from random-effect model analysis (see Supplemental Content Fig. S3, which illustrates the Sensitivity analyses of fixed-effect model analysis of treatment success without modification, http://links.lww.com/MD/D588). In a subgroup analysis including studies only of population at TOC and LFU visit, clinical treatment success showed no significant difference between arms and the result was imprecise (see Supplementary Content Fig. S4, http://links.lww.com/MD/D589 and S5, http://links.lww.com/MD/D590, which illustrates the subgroup analyses of clinical treatment success for population at TOC visit and LFU visit).

4.2. Microbiological treatment success

Eighteen studies including 5050 patients were involved in the investigation concerning the effect of microbiological treatment success at end of treatment with different antimicrobial agents. Comparing different carbapenem antibiotics, the result was imprecise and there was no significant difference between arms. The network plots of eligible comparisons for microbiological treatment success are shown in Fig. 2(B). The funnel plots showed no asymmetry (see Supplementary Content Fig. S6, which illustrates the funnel plots of microbiological treatment success, http://links.lww.com/MD/D591).

For the rest, CFPM have significantly lower microbiological treatment success rate compared to BAPM, CA, ceftriaxone (CTAX), DOPM, ETPM, IC, ICRB, LEFC, MEPM, MV, and PT (RR = 1.74, 95% CrI 1.17–3.56; RR = 1.78, 95% CrI 1.19–3.65; RR = 1.84, 95% CrI 1.23–3.81; RR = 1.74, 95% CrI 1.16–3.58; RR = 1.89, 95% CrI 1.27–3.90; RR = 1.69, 95% CrI 1.14–3.47; RR = 1.68, 95% CrI 1.13–3.44; RR = 1.54, 95% CrI 1.03–3.18; RR = 1.85, 95% CrI 1.23–3.78; RR = 1.84, 95% CrI 1.25–3.77; RR = 1.82, 95% CrI 1.24–3.71, respectively; Fig. 4 and Table 2). LEFC have significantly lower microbiological treatment success rate compared to CA, DOPM, MEPM, and MV (RR = 1.15, 95% CrI 1.09–1.22; RR = 1.13, 95% CrI 1.09–1.18; RR = 1.20, 95% CrI 1.01–1.41; RR = 1.20, 95% CrI 1.01–1.41, respectively; Fig. 4 and Table 2).

The result from sensitivity analyses with studies using fixed-effect model analysis almost replicated the result from random-effect model analysis (see Supplementary Content Fig. S7, which illustrates the sensitivity analyses of fixed-effect model analysis of microbiological treatment success, http://links.lww.com/MD/D592). In a subgroup analysis including studies only for population at TOC and LFU visit, clinical treatment success showed no significant difference between arms and the result was imprecise (see Supplementary Content Fig. S8, http://links.lww.com/MD/D593 and S9, http://links.lww.com/MD/D594, which illustrates the subgroup analyses of microbiological treatment success for population at TOC visit and LFU visit).

4.3. AEs

Among the 11 included studies, 4871 patients experienced any AEs. Risk of any AEs was higher in the IC arm compared with the seven MEPM treatment arms (RR = 3.01, 95% CrI 1.10–8.70) (see Supplementary Content Fig. S10, which illustrates the risk of

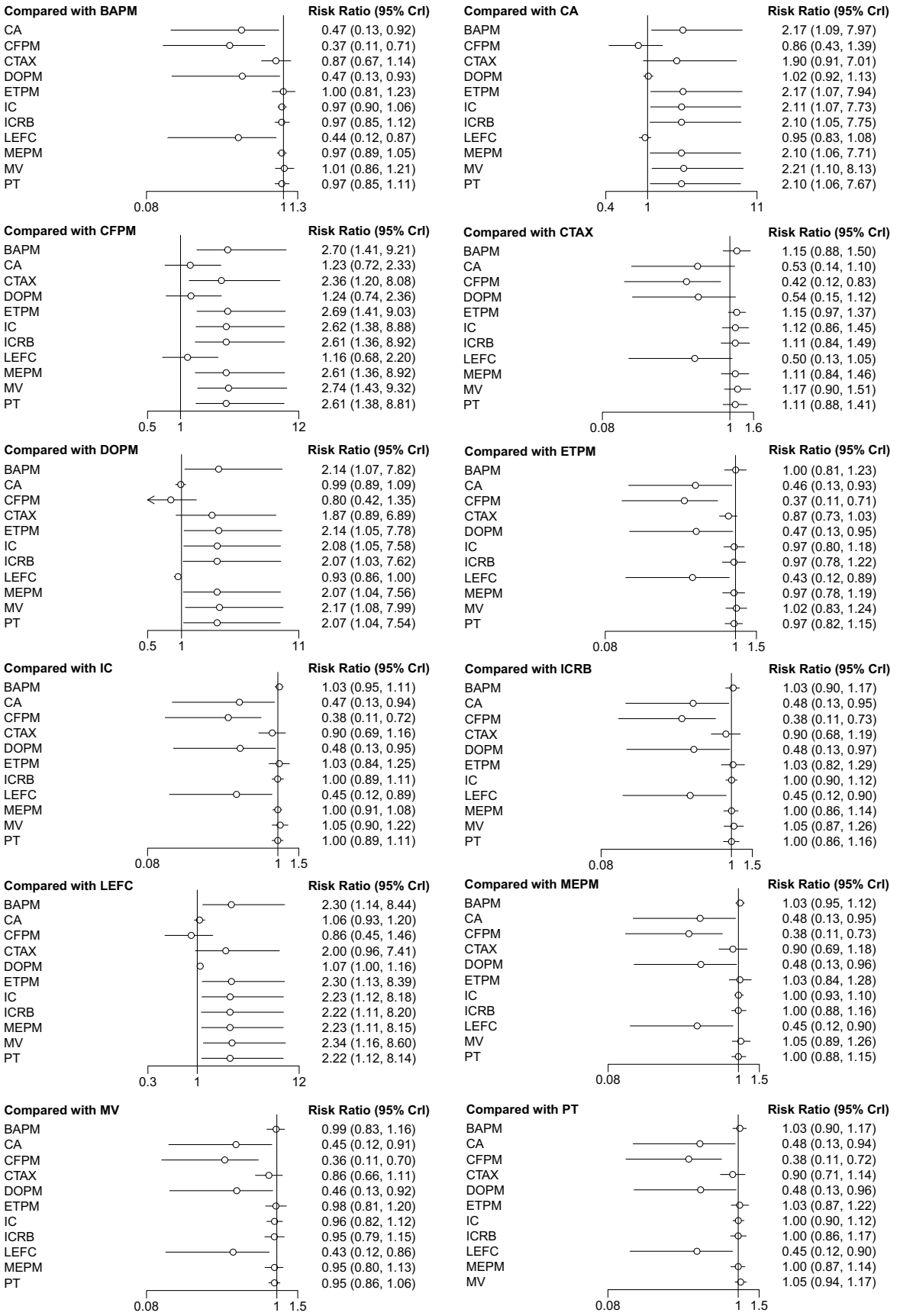

Figure 3. The effect of carbapenems vs alternative antimicrobial agents on clinical treatment success.

Table 2

RRs and 95% CrI for clinical treatment success and microbiological treatment success.

Clinical treatment success	BAPM	0.47 (0.13, 0.92)	0.37 (0.11, 0.71)	0.87 (0.67, 1.14)	0.47 (0.13, 0.93)	1.00 (0.81, 1.23)	0.97 (0.90, 1.06)	0.97 (0.85, 1.12)	0.44 (0.12, 0.87)	0.97 (0.89, 1.05)	1.01 (0.86, 1.21)	0.97 (0.85, 1.11)
	2.17 (1.09, 7.97)	CA	0.86 (0.43, 1.39)	1.90 (0.91, 7.01)	1.02 (0.92, 1.13)	2.17 (1.07, 7.94)	2.11 (1.07, 7.73)	2.10 (1.05, 7.75)	0.95 (0.83, 1.08)	2.10 (1.06, 7.71)	2.21 (1.10, 8.13)	2.10 (1.06, 7.67)
	2.70 (1.41, 9.21)	1.23 (0.72, 2.33)	CFPM	2.36 (1.20, 8.08)	1.24 (0.74, 2.36)	2.69 (1.41, 9.03)	2.62 (1.38, 8.88)	2.61 (1.36, 8.92)	1.16 (0.68, 2.20)	2.61 (1.36, 8.92)	2.74 (1.43, 9.32)	2.61 (1.38, 8.81)
	1.15 (0.88, 1.50)	0.53 (0.14, 1.10)	0.42 (0.12, 0.83)	CTAX	0.54 (0.15, 1.12)	1.15 (0.97, 1.37)	1.12 (0.86, 1.45)	1.11 (0.84, 1.49)	0.50 (0.13, 1.05)	1.11 (0.84, 1.46)	1.17 (0.90, 1.51)	1.11 (0.88, 1.41)
	2.14 (1.07, 7.82)	0.99 (0.89, 1.09)	0.80 (0.42, 1.35)	1.87 (0.89, 6.89)	DOPM	2.14 (1.05, 7.78)	2.08 (1.05, 7.58)	2.07 (1.03, 7.62)	0.93 (0.86, 1.00)	2.07 (1.04, 7.56)	2.17 (1.08, 7.99)	2.07 (1.04, 7.54)
	1.00 (0.81, 1.23)	0.46 (0.13, 0.93)	0.37 (0.11, 0.71)	0.87 (0.73, 1.03)	0.47 (0.13, 0.95)	ETPM	0.97 (0.80, 1.18)	0.97 (0.78, 1.22)	0.43 (0.12, 0.89)	0.97 (0.78, 1.19)	1.02 (0.83, 1.24)	0.97 (0.82, 1.15)
	1.03 (0.95, 1.11)	0.47 (0.13, 0.94)	0.38 (0.11, 0.72)	0.90 (0.69, 1.16)	0.48 (0.13, 0.95)	1.03 (0.84, 1.25)	IC	1.00 (0.89, 1.11)	0.45 (0.12, 0.89)	1.00 (0.91, 1.08)	1.05 (0.90, 1.22)	1.00 (0.89, 1.11)
	1.03 (0.90, 1.17)	0.48 (0.13, 0.95)	0.38 (0.11, 0.73)	0.90 (0.68, 1.19)	0.48 (0.13, 0.97)	1.03 (0.82, 1.29)	1.00 (0.90, 1.12)	ICRB	0.45 (0.12, 0.90)	1.00 (0.86, 1.14)	1.05 (0.87, 1.26)	1.00 (0.86, 1.16)
	2.30 (1.14, 8.44)	1.06 (0.93, 1.20)	0.86 (0.45, 1.46)	2.00 (0.96, 7.41)	1.07 (1.00, 1.16)	2.30 (1.13, 8.39)	2.23 (1.12, 8.18)	2.22 (1.11, 8.20)	LEFC	2.23 (1.11, 8.15)	2.34 (1.16, 8.60)	2.22 (1.12, 8.14)
	1.03 (0.95, 1.12)	0.48 (0.13, 0.95)	0.38 (0.11, 0.73)	0.90 (0.69, 1.18)	0.48 (0.13, 0.96)	1.03 (0.84, 1.28)	1.00 (0.93, 1.10)	1.00 (0.88, 1.16)	0.45 (0.12, 0.90)	MEPM	1.05 (0.89, 1.26)	1.00 (0.88, 1.15)
	0.99 (0.83, 1.16)	0.45 (0.12, 0.91)	0.36 (0.11, 0.70)	0.86 (0.66, 1.11)	0.46 (0.13, 0.92)	0.98 (0.81, 1.20)	0.96 (0.82, 1.12)	0.95 (0.79, 1.15)	0.43 (0.12, 0.86)	0.95 (0.80, 1.13)	MV	0.95 (0.86, 1.06)
	1.03 (0.90, 1.17)	0.48 (0.13, 0.94)	0.38 (0.11, 0.72)	0.90 (0.71, 1.14)	0.48 (0.13, 0.96)	1.03 (0.87, 1.22)	1.00 (0.90, 1.12)	1.00 (0.86, 1.17)	0.45 (0.12, 0.90)	1.00 (0.87, 1.14)	1.05 (0.94, 1.17)	PT
Microbiological treatment success	BAPM	1.01 (0.90, 1.18)	0.57 (0.28, 0.85)	1.06 (0.89, 1.27)	0.99 (0.87, 1.16)	1.08 (0.92, 1.30)	0.97 (0.92, 1.03)	0.96 (0.89, 1.05)	0.88 (0.77, 1.03)	1.05 (0.98, 1.16)	1.06 (0.96, 1.18)	1.05 (0.96, 1.15)
	0.99 (0.85, 1.11)	CA	0.56 (0.27, 0.84)	1.04 (0.83, 1.28)	0.98 (0.94, 1.02)	1.07 (0.86, 1.31)	0.96 (0.83, 1.07)	0.95 (0.81, 1.08)	0.87 (0.82, 0.92)	1.04 (0.89, 1.20)	1.05 (0.88, 1.21)	1.03 (0.88, 1.18)
	1.74 (1.17, 3.56)	1.78 (1.19, 3.65)	CFPM	1.84 (1.23, 3.81)	1.74 (1.16, 3.58)	1.89 (1.27, 3.90)	1.69 (1.14, 3.47)	1.68 (1.13, 3.44)	1.54 (1.03, 3.18)	1.85 (1.23, 3.78)	1.84 (1.25, 3.77)	1.82 (1.24, 3.71)
	0.95 (0.79, 1.12)	0.96 (0.78, 1.20)	0.54 (0.26, 0.81)	CTAX	0.94 (0.76, 1.18)	1.03 (1.00, 1.06)	0.92 (0.77, 1.08)	0.91 (0.75, 1.09)	0.83 (0.67, 1.04)	1.00 (0.82, 1.21)	1.01 (0.85, 1.17)	0.99 (0.84, 1.15)
	1.01 (0.86, 1.15)	1.02 (0.98, 1.07)	0.57 (0.28, 0.86)	1.06 (0.85, 1.31)	DOPM	1.09 (0.87, 1.35)	0.98 (0.84, 1.10)	0.97 (0.83, 1.11)	0.89 (0.85, 0.92)	1.06 (0.90, 1.24)	1.07 (0.90, 1.24)	1.05 (0.89, 1.22)
	0.92 (0.77, 1.09)	0.94 (0.76, 1.16)	0.53 (0.26, 0.79)	0.97 (0.94, 1.00)	0.97 (0.74, 1.14)	ETPM	0.90 (0.75, 1.05)	0.89 (0.74, 1.05)	0.81 (0.65, 1.01)	0.98 (0.80, 1.17)	0.98 (0.83, 1.13)	0.97 (0.82, 1.11)
	1.03 (0.98, 1.08)	1.04 (0.93, 1.20)	0.59 (0.29, 0.87)	1.08 (0.92, 1.30)	1.02 (0.91, 1.19)	1.11 (0.95, 1.33)	IC	0.99 (0.93, 1.06)	0.90 (0.80, 1.06)	1.09 (1.00, 1.19)	1.09 (1.00, 1.20)	1.07 (1.00, 1.17)
	1.04 (0.96, 1.13)	1.05 (0.93, 1.23)	0.60 (0.29, 0.89)	1.10 (0.92, 1.33)	1.03 (0.90, 1.21)	1.13 (0.95, 1.36)	1.01 (0.95, 1.07)	ICRB	0.91 (0.79, 1.08)	1.10 (0.99, 1.23)	1.10 (0.99, 1.23)	1.09 (0.99, 1.20)
	1.14 (0.97, 1.31)	1.15 (1.09, 1.22)	0.65 (0.31, 0.97)	1.20 (0.96, 1.49)	1.13 (1.09, 1.18)	1.23 (0.99, 1.53)	1.11 (0.95, 1.26)	1.09 (0.93, 1.26)	LEFC	1.20 (1.01, 1.40)	1.20 (1.01, 1.41)	1.19 (1.00, 1.38)
	0.95 (0.86, 1.02)	0.96 (0.83, 1.13)	0.54 (0.26, 0.82)	1.00 (0.83, 1.21)	0.94 (0.81, 1.11)	1.03 (0.85, 1.24)	0.92 (0.84, 1.00)	0.91 (0.82, 1.01)	0.83 (0.71, 0.99)	MEPM	1.00 (0.88, 1.13)	0.99 (0.88, 1.11)
	0.94 (0.85, 1.04)	0.96 (0.83, 1.13)	0.54 (0.27, 0.80)	0.99 (0.86, 1.18)	0.94 (0.80, 1.11)	1.02 (0.88, 1.21)	0.92 (0.84, 1.00)	0.91 (0.81, 1.01)	0.83 (0.71, 0.99)	1.00 (0.88, 1.13)	MV	0.99 (0.94, 1.03)
	0.96 (0.87, 1.05)	0.97 (0.84, 1.14)	0.55 (0.27, 0.81)	1.01 (0.87, 1.19)	0.95 (0.82, 1.12)	1.03 (0.90, 1.21)	0.93 (0.86, 1.00)	0.92 (0.83, 1.01)	0.84 (0.72, 1.00)	1.01 (0.90, 1.14)	1.01 (0.97, 1.06)	PT

BAPM = biapenem, CA = ceftazidime/avibactam, CFPM = cefepime, CTAX = ceftriaxone, DOPM = doripenem, ETPM = ertapenem, IC = imipenem/cilastatin, LEFC = levofloxacin, MEPM = meropenem, MV = meropenem/vaborbactam, PT = piperacillin/tazobactam, RB = relebactam.

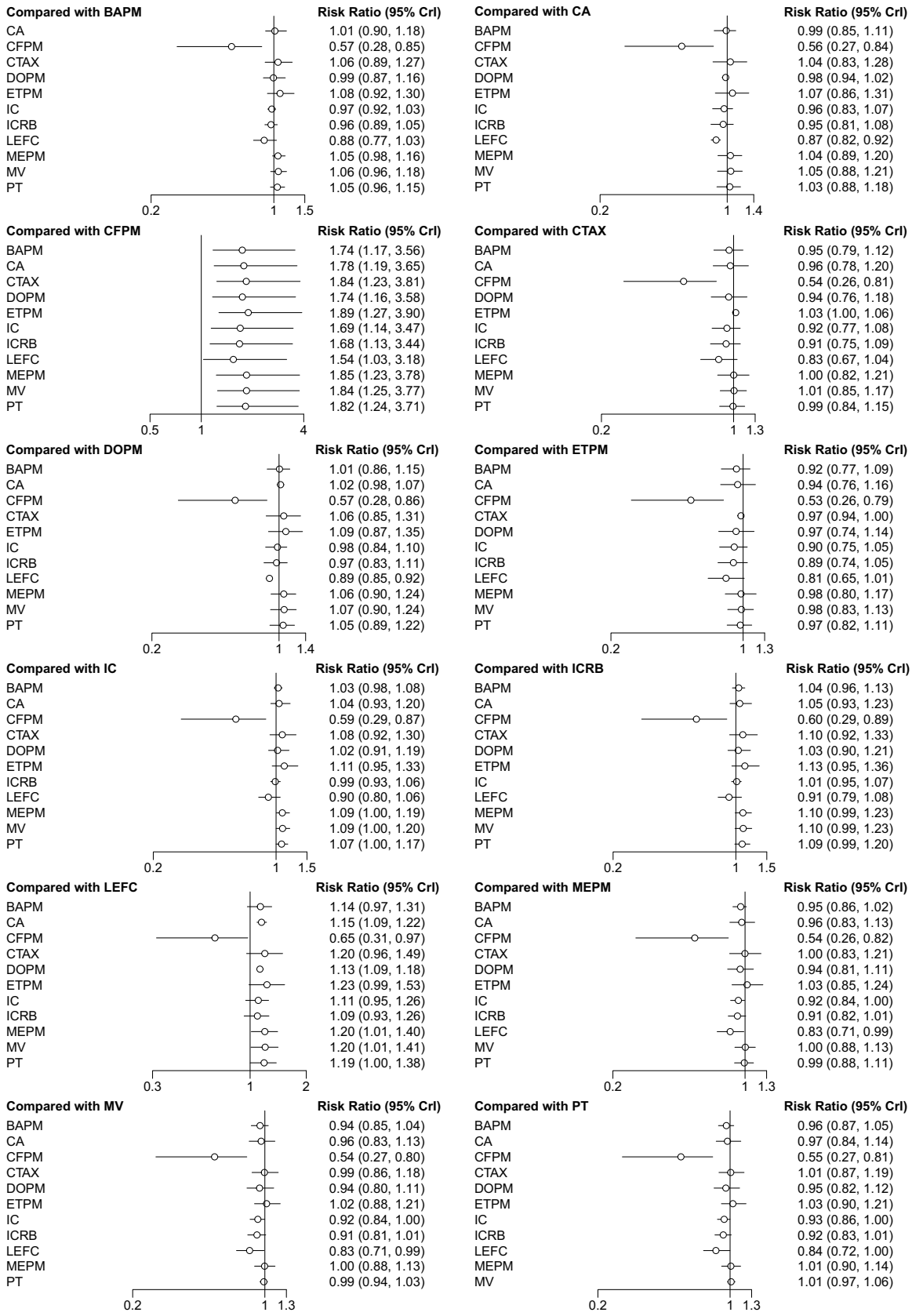

Figure 4. The effect of carbapenems vs alternative antimicrobial agents on microbiological treatment success.

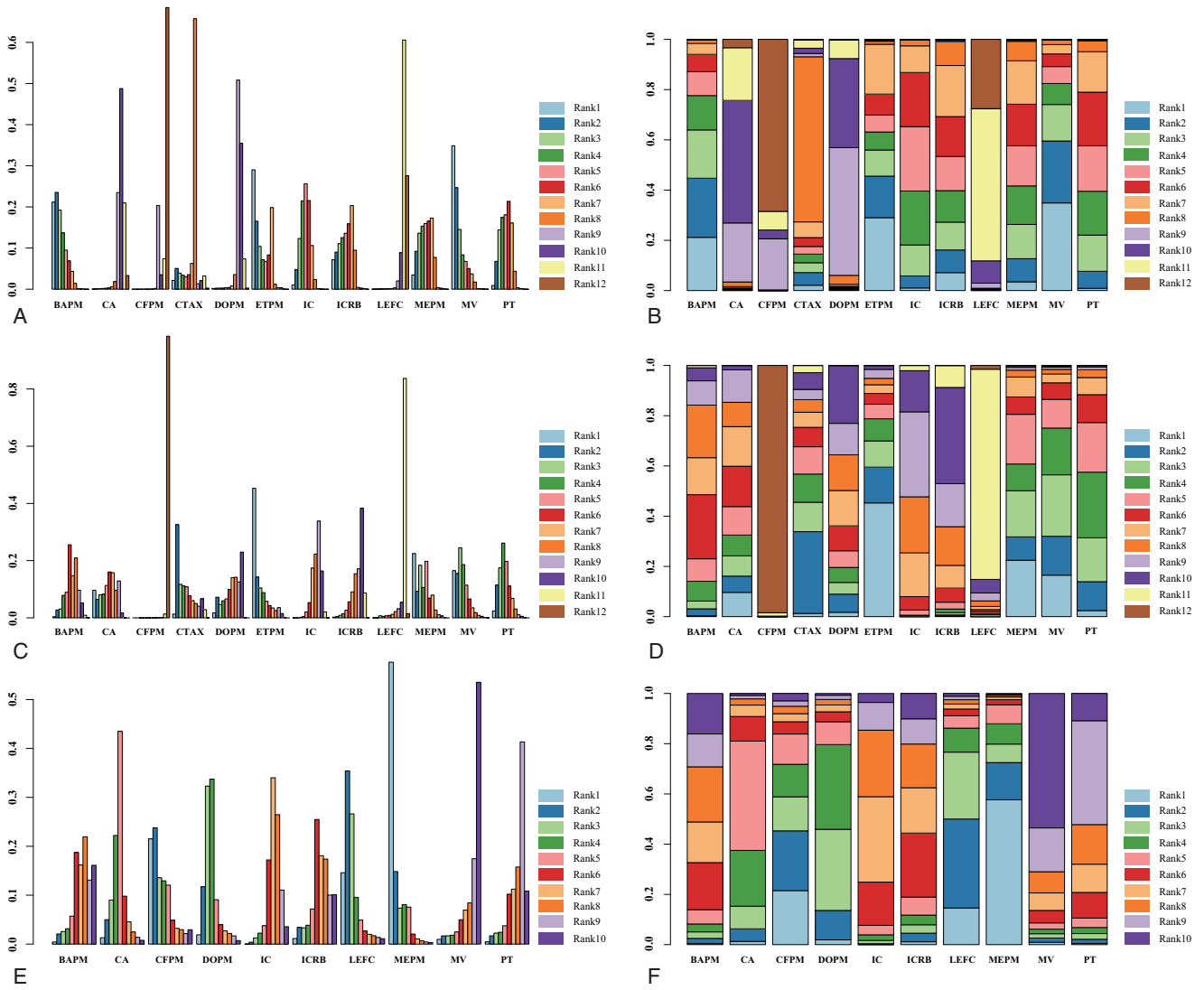

Figure 5. Rank probabilities and cumulative rank plots for effective outcomes. (A) rank probability for clinical treatment success; (B) cumulative rank plot for clinical treatment success; (C) rank probability for microbiological treatment success; (D) cumulative rank plot for microbiological treatment success; (E) rank probability for adverse events; (F) cumulative rank plot for adverse events.

AEs of carbapenems vs alternative antimicrobial agents, http://links.lww.com/MD/D595).

4.4. Relative ranking of carbapenems and other antimicrobial agents

In secondary analyses, we compared the estimated rank probabilities of different carbapenems and other antimicrobial agents. The results are shown in Fig. 5 and Table S2 (Supplemental Content Table S2, which illustrates the detailed rank probability, http://links.lww.com/MD/D597). As a result, the cumulative rank probability of clinical treatment success at end of treatment showed that MV, ETPM, and BAPM had a relatively higher, and DOPM, CA, LEFC, and CFPM a relatively lower, clinical treatment success rate. On the other hand, the cumulative rank probability results of microbiological treatment success indicated that ETPM, CTAX, and MV had a higher microbiological treatment success rate, whereas CFPM and LEFC showed lower microbiological treatment success rate.

4.5. Comparisons between direct and indirect evidences

When a loop connecting three arms existed, the node-splitting method was used to calculate the inconsistency of the model. The method separated the evidence concerning certain comparisons into direct and indirect evidence, and the inconsistency was reported by its Bayesian *P* value. For the majority of our results, most of the *P* values from the node-splitting method were above .05, which indicated minor differences between the direct and indirect evidence. However, significant differences were observed at the comparison, which limited the use of our results. For example, when we compared PT and CFPM for their effect in clinical treatment success, both the pooled RR combining both direct and indirect evidence indicated a higher clinical treatment success rate of PT compared with CFPM, whereas RR from direct and indirect evidence showed a significant difference. Nevertheless, no significant difference between direct and indirect evidence was observed in clinical treatment success and microbiological treatment success (Fig. 6).

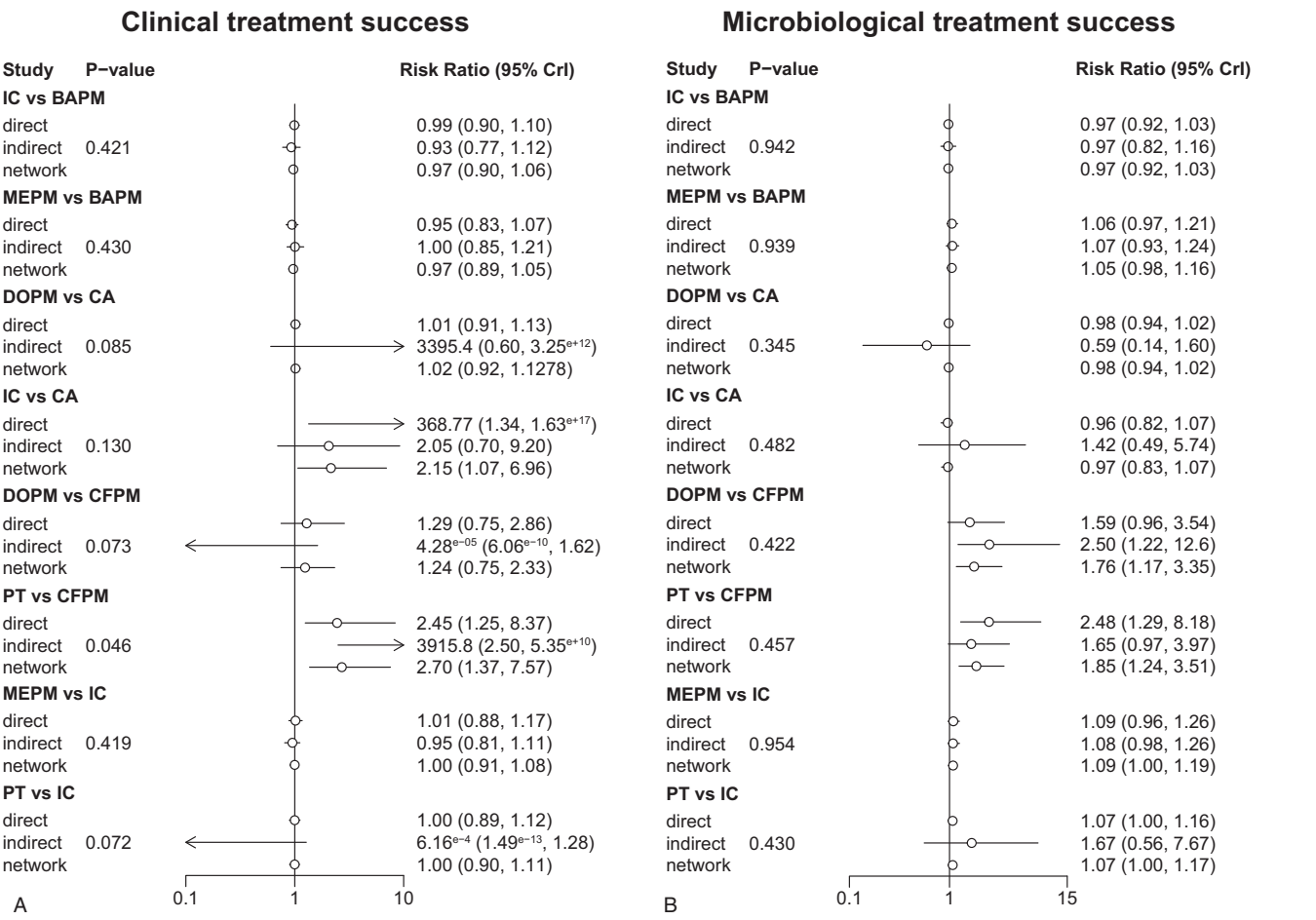

Figure 6. Comparison between direct and indirect evidence, (A) clinical treatment success, (B) microbiological treatment success.

5. Discussion

In this meta-analysis, we systematically reviewed and evaluated the efficacy and safety of carbapenems compared with alternative antibiotics for treatment of cUTI. Previous systematic reviews and traditional meta-analysis have not investigated all carbapenems for treatment of cUTI.[20,47] Furthermore, we provide a joint assessment of drug efficacy and adverse effects for each carbapenem antibiotic relative to the others.

To the best of our knowledge, this is the first network meta-analysis considering the efficacy and safety of carbapenems with alternative antibiotics for treatment of cUTI. The study has several key findings. First, MV, ETPM, and BAPM had better clinical treatment success, whereas DOPM had a lower relatively clinical treatment success rate. Second, ETPM and MV had better microbiological treatment success. Finally, IC and MV were associated with increased risk of AEs, but MEPM showed lower risk of AEs.

Balancing the evidence for drug efficacy, the novel carbapenem/β-lactamase inhibitor combination MV, appears to be the best available treatment for carbapenem-resistant cUTI. Therefore, it is reasonable to consider that MV is one of the best carbapenems/β-lactamase inhibitor for cUTI. However, MV showed a relatively high rate of AEs. cUTIs are increasingly caused by multidrug-resistant Gram-negative pathogens, with observed rates of extended-spectrum β-lactamase-producing *Escherichia coli* and carbapenem-resistant *Enterobacteriaceae* rising steadily over the last decade.[48,49] MV, recently approved for the treatment of cUTI and acute pyelonephritis, offers potent activity against common multidrug-resistant Gram-negative uropathogens, particularly carbapenem-resistant *Enterobacteriaceae*.[10,16]

ETPM, BAPM, IC, ICRB, and MEPM showed a similar treatment success rate to that of MV for treatment of cUTI. However, ETPM and BAPM had lower rates of side effects. Compared with other antimicrobial agents, ETPM, BAPM, and MEPM showed higher treatment success rates and similar AEs. Therefore, ETPM, BAPM, and MEPM is another reasonable choice for cUTI empiric therapy.

DOPM was associated with the poorest outcome in clinical treatment success of cUTI compared with other carbapenems. DOPM had similar clinical treatment success to CA in treatment of cUTI reported by Chen.[20] However, considering the limited power of the included study, these results are not promising. Further research and high-quality RCTs are needed to confirm this finding.

The present meta-analysis is subject to several limitations. Overall, the quality of RCTs was moderate, and we did not exclude any studies based on risk of bias assessment and sample size studies. Given the challenges in searching for such studies, we restricted the identification of inappropriate antimicrobial treatment to studies identified in this systematic review, which

resulted in a heterogeneous group of subjects with uncomplicated UTI, acute pyelonephritis, and cUTI. In addition, the definitions of cUTI and treatment success evaluate time were notably different across studies. The majority of included patients were adults and only a few included patients were children, so caution should be used in applying the results to children. The limited number of studies may result in an exaggerated clinical curative effect. Thus, our findings should be interpreted with caution; large and high-quality RCTs are needed to confirm our findings. Some unpublished articles and missing data might be another source of bias. Finally, we were not able to estimate the impact that the different drugs could have on the global public health burden or the impact on the emerging problem of carbapenem-resistant cUTI. Thus, individual centers should select the best therapy regimens according to local epidemiology and susceptibility patterns.

6. Conclusions

In sum, we carried out a systematic review and network meta-analysis to compare efficacy and safety of carbapenems for cUTI. Nineteen RCTs studies involving 7380 participants were included in the analysis. the novel carbapenem and β-lactamase inhibitor combination MV was associated with a higher treatment success rate for cUTI, especially for carbapenem-resistant cUTI. However, MV showed higher risk of AEs. ETPM, BAPM, MEPM showed a similar treatment success rate to MV, with less risk of AEs. IC and ICRB showed a similar treatment success rate MV. However, IC and ICRB are associated with frequent occurrences of AEs. We provide evidence in favor of the adoption of MV as a first-choice treatment of carbapenem-resistant cUTI, and ETPM, BAPM, and MEPM as another reasonable choice for cUTI empiric therapy. This therapeutic option is supported by available clinical data from different sources. Our research should be regarded as crucial evidence to help formulate clinical decisions in choosing a treatment regimen for cUTI.

Author contributions

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