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Carbapenems vs tigecycline for the treatment of complicated intra-abdominal infections

A Bayesian network meta-analysis of randomized clinical trials

Lingyuan Chen, BS[a], Xueyan Liang, MM[a], Junsong Jiang, MM[b], Xianshu Li, BS[a], Yan Li, MM[a,*]

Abstract

Background: Complicated intra-abdominal infections (cIAIs) are common in clinical practice, caused by a mixture of aerobic and anaerobic bacteria, increase the risk of mortality. Carbapenems and tigecycline (TGC) are recommended for antimicrobial therapies for cIAIs.

Objective: To compare the effectiveness and safety of different carbapenems vs TGC for the treatment of cIAIs.

Methods: PubMed, Embase, Medline (via Ovid SP) and Cochrane library databases were systematically searched. We included randomized controlled trials (RCTs) comparing different carbapenems vs TGC for the treatment of cIAIs. The pooled odds ratio (OR) with 95% credible interval (CrI) was calculated by Markov chain Monte Carlo methods. We estimated summary ORs using pairwise and network meta-analysis with random effects.

Results: Fifteen studies involving 6745 participants were included in the analysis. Five different carbapenems and TGC were ultimately evaluated in this study. Although, the efficacy of carbapenems and TGC by ORs with corresponding 95% CrIs had not yet reached statistical differences, the cumulative rank probability indicated that clinical treatment success from best to worst was doripenem (DOPM), meropenem (MEPM), imipenem/cilastatin (IC), biapenem (BAPM), TGC and imipenem/cilastatin/relebactam (ICRB); microbiological treatment success from best to worst was DOPM, MEPM, IC, BAPM, ICRB and TGC. As for the risk of adverse events (AEs), TGC showed higher risk of AEs compared with IC (OR = 1.53, 95% CrI = 1.02–2.41), the remain antibiotic agents from lower to higher was MEPM, IC, BAPM, DOPM, ICRB and TGC. The risk of mortality from lower to higher was BAPM, DOPM, MEPM, IC, TGC and ICRB.

Conclusion: No differences in clinical and microbiological outcomes were observed between different carbapenems and TGC. Balancing the evidence for drug efficacy and side effects, DOPM appears to be the best available treatment for cIAIs. Therefore, it is reasonable to consider that DOPM is one of the best carbapenem monotherapy for cIAIs. MEPM and IC was also associated with higher rates of clinical and microbiological treatment success following DOPM. Empiric antimicrobial treatment of patients with cIAIs should be selected in light of the local bacterial epidemiology and patterns of resistance.

Abbreviations: AEs = adverse events, BAPM = biapenem, CI = confidential interval, cIAIs = complicated intra-abdominal infections, CrI = credible interval, DOPM = doripenem, IC = imipenem/cilastatin, ICRB = imipenem/cilastatin/relebactam, MEPM = meropenem, OR = odds ratio, RCT = randomized controlled trial, SUCRA = the surface under the cumulative ranking curve, TGC = tigecycline.

Keywords: carbapenems, complicated intra-abdominal infections, meta-analysis, tigecycline

1. Introduction

Complicated intra-abdominal infections (cIAIs) are challenging and common in clinical practice and universal reason for hospital stay, often caused by a mixture of aerobic and anaerobic bacteria, increase the risk of mortality.[1] Intra-abdominal infections with range of spectrum of diseases, from simple peritonitis or appendicitis to complicated diverticulosis or intestinal perforation and other penetrating intra-abdominal injuries.[2,3] Intra-abdominal infections are caused by multiple microorganisms, common samples are Gram-negative pathogens, mainly associated with normal enteric flora *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.[2,4] Patients with hospital acquired infections may possess multiple resistance, such as extended-spectrum β-lactamases.[5–7]

The outcome of cIAIs, depends on the severity of the illness, extending beyond the wall of a hollow organ, and the timely diagnosis and treatment, involving operative interventions, as well as selection of appropriate antimicrobial therapy.[8] The timing of antibiotic treatment also affects the duration of hospital stay, even mortality, especially delays in antibiotic administration

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[a] Department of Pharmacy, [b] Department of Reproductive Medicine, The People's Hospital of Hechi, Hechi, PR China.

[*] Correspondence: Yan Li, Department of Pharmacy, The People's Hospital of Hechi, Hechi, PR China (e-mail: liyan20102010@outlook.com).

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upon arrival at hospital.[9–11] The antimicrobial therapies recommended for cIAIs in the guidelines by the Surgical Infection Society and Infectious Diseases Society of America, the World Society of Emergency Surgery include carbapenem and tigecycline (TGC).[4,12,13]

Carbapenems have been proven to have wider spectrum against bacteria in comparison with the available penicillin, cephalosporin, and β-lactam/β-lactamase inhibitor combinations. Carbapenems also have a low propensity for the selection of mutants that are highly resistant to broad-spectrum cephalosporins.

TGC is an expanded broad-spectrum intravenous glycylcycline antibiotic, meeting the urgent need of overcoming the worsening antimicrobial resistance by surmounting the ribosomal protection and active drug efflux resistance mechanism,[14,15] with in vitro activity against bacterial pathogens associated with intra-abdominal infections.[16,17]

TGC showed non-inferior to imipenem/cilastatin (IC) in previous studies for treatment of cIAIs.[18,19] With the extensive clinical use of carbapenems and TGC in cIAIs, more randomized controlled trials (RCTs) on this topic have been published. However, systematic reviews and meta-analyses of these antibiotic therapies are limited. In general, carbapenems having different antibacterial activity such as imipenem, doripenem (DOPM) and panipenem were effective against Gram-positive bacteria, while meropenem (MEPM), biapenem (BAPM), DOPM and ertapenem were a little bit effective against Gram-negative organisms.[20] Although carbapenems have documented efficacy in the treatment of cIAIs, it is unclear if this effect of different carbapenems based regimen across the range of published studies, especially in the times of rising antibiotic resistance. Due to the current lack of new antibiotic agents without overlapping mechanisms of resistance, judicious use of these broad-spectrum agents for treatment of resistant Gram-negative infections is critical to preserve their future utility. Network meta-analysis has enabled the comparison of multiple treatment arms by combining evidence from direct comparisons of 2 treatments and evidence from indirect comparisons based on a common comparator. The main aim of the current study is to compare the effectiveness and safety of different carbapenem and TGC treatments for cIAIs. For this purpose, we assessed clinical and microbiological treatment success without antibiotics modification as the primary endpoint. Death and adverse events (AEs) were also assessed as the secondary outcomes.

2. Materials and methods

The study was approved by the ethics institutional review board of the The People's Hospital of Hechi. This study was conducted was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

2.1. Search strategy and selection criteria

PubMed, Embase, Medline (via Ovid SP), and Cochrane library databases database up to February 2019 were systematically searched. The following search terms were used: 'complicated intra-abdominal infections', 'cIAIs', '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:

(1) population: patients with cIAIs;
(2) intervention: patients therapy with carbapenems or TGC;
(3) comparison: placebo or other regimen of carbapenems or TGC;
(4) outcome: primary outcomes: clinical and microbiological treatment success; secondary outcomes: AEs; mortality;
(5) design: RCTs.

2.3. Exclusion criteria

The exclusion criteria were

(1) reviews, nonclinical studies and case observations;
(2) not RCTs;
(3) reduplicated studies;
(4) improper outcome measures;
(5) meta-analysis, case reports, and editorials.

2.4. Selection of studies and data extraction

Comprehensive search of databases were performed by three researchers (Chen, Liang and Jiang), 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, year of publication, number of patients, age category (adult or child), interventions, comparisons, and outcomes.

2.5. Risk of bias assessment

Three reviewers (Chen, Liang, and Jiang) 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.[21,22] In terms of the assessment criteria, each study was rated and assigned to one of the three 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 were not met, or not included, the study was deemed to have a high risk of bias.[21,23]

2.6. Data analysis

For studies published more than once (ie, duplicates), we included only the report with the most informative and complete data. Traditional pairwise meta-analysis was performed to combine studies addressing the same outcome and antibacterial agents; the results were evaluated by the odds ratio (OR) with 95%

confidential interval (CI). Test of heterogeneity were conducted with the Cochran's Q statistic and using I^2 tests.[24,25] A value of I^2 greater than 50% to indicate substantial heterogeneity and sought the potential sources of heterogeneity, such as clinical heterogeneity and methodological heterogeneity.[21] Traditional pairwise meta-analysis were also used for exploratory estimates of drug efficacy, using the R package 'meta' (version 4.9-4) and random-effects model was used.[26]

In addition to pair-wise meta-analyses making direct comparison between different carbapenems or TGC, a network meta-analysis concerning multiple treatments was performed with a random-effect model within a Bayesian framework. We fitted all models in OpenBUGS (version 3.2.2)[27] using the binomial likelihood for dichotomous outcomes, uninformative prior distributions for the treatment effects, and a minimally informative prior distribution for the common heterogeneity SD. Nodes of BAPM, DOPM, IC, imipenem/cilastatin/relebactam (ICRB), MEPM and TGC were included in the network analysis. Ten thousand simulations were set up initially for each chain as the 'burn-in' period, yielding 200,000 iterations to get the ORs and corresponding 95% credible intervals (CrIs) of model parameters, while three Markov chains were run simultaneously. Convergence of models was ensured by visual inspection of three chains and after considering the Brooks-Gelman-Rubin diagnostic, trace plot and density plot.[28]

To rank the treatments for each outcome, we used the surface under the cumulative ranking curve (SUCRA) and the mean ranks, SUCRA would be 100% when a treatment is certain to be the best and 0 when a treatment is certain to be the worst, and higher posterior probabilities in each simulation indicates the higher chance of being the best treatment regimen.[29,30]

We performed sensitivity analyses based on studies with Low risk of selection bias for concealment and excluding studies with small sample size (at the 25th percentile).[31,32] The publication bias was evaluated by funnel plot calculated by STATA 14.0 (Stata Corp, College Station, TX) software.

3. Results

3.1. Study identification and selection

A total of 1542 records were retrieved from the initial database search. After removing 512 duplicate articles, 1030 records were eligible. Based on the inclusion and exclusion criteria, 987 articles were excluded after a simple reading of the titles and abstracts of the articles. The remaining 43 full-text articles were assessed for eligibility. Furthermore, not a relevant study design, not RCT, meta-analysis, no outcomes were excluded. Finally, a total of 15 RCTs studies were included in the meta-analysis (Table 1).[3,18,19,33–44] The selection process is shown in Fig. 1.

3.2. Study characteristics

The basic characteristics of the included studies are listed in Table 1, and the definition of clinical and microbiological and timing of evaluation are showed in Table S1 (Supplemental Content Table S1, http://links.lww.com/MD/D266, which illustrates the definition of clinical and microbiological and timing of evaluation). Fifteen RCTs studies involving 6745 participants were included in the analysis. These studies were published from 1993 to 2016. The number of participants in the studies ranged from 41 to 1759. All included studies adopted a 2-arm designs. Among the 30 arms in 15 trials, BAPM, DOPM, IC, ICRB, MEPM, and TGC were evaluated in 1, 2, 13, 1, 7, 6 arms, respectively. The definitions of cIAIs and clinical and microbiological outcomes were summarized in the Table S1 (Supplemental Content Table S1, http://links.lww.com/MD/D266, which illustrates the definition of clinical and microbiological and timing of evaluation).

3.3. Risk of bias assessment

The outcomes of the risk of bias are summarized in Fig. S1A and S1B (Supplemental Content Fig. S1, http://links.lww.com/MD/D266, which illustrates the outcomes of the risk of bias of included studies). Almost half of the included RCTs were assessed to be of a high methodological quality. Six studies had low risk for sequence generation and allocation concealment.[19,34,35,38,42,43] Seven studies were performed in open-label model, with a high risk for performance bias and detection bias.[33–35,37,40,41,44] As for attrition bias, 2 studies had unclear risk with insufficient details for patient dropouts.[34,35] Most RCTs were at low risk for the reporting bias.

3.4. Clinical treatment success

Fourteen studies including a total of 4799 patients provided data on clinical treatment success. Network plots are shown in Fig. 2A. The efficacy of clinical treatment success of different carbapenems and TGC by ORs and corresponding 95% CrIs was showed in Fig. 3A. As a result, the efficacy of different carbapenems and TGC by ORs and corresponding 95% CrIs had not yet reached statistical differences, the cumulative ranking curve (SUCRA) probability indicated that clinical treatment success from best to worst was DOPM, MEPM, IC, BAPM, ICRB and TGC (Fig. 4A and B).

Sensitivity analyses with studies with Low risk of selection bias for concealment and excluding studies with small sample size were showed similar results and presented in the Figure S2 (Supplemental Content Fig. S2, http://links.lww.com/MD/D266, which illustrates the forest plot of sensitivity analysis of clinical treatment success by low risk of selection bias for concealment) and Figure S3 (Supplemental Content Fig. S3, http://links.lww.com/MD/D266, which illustrates the forest plot of sensitivity analysis of clinical treatment success by excluding studies with small sample size).

3.5. Microbiological treatment success

Microbiological treatment success was evaluated by 4238 investigators in the 15 trials. Network plots are shown in Fig. 2B. The efficacy of microbiological treatment success of different carbapenems and TGC by ORs and corresponding 95% CrIs was showed in Fig. 3B. Probabilities of rankings and SUCRAs of the treatment strategies in terms of microbiolog cal treatment success are summarized in Fig. 4C and D and indicated that microbiological treatment success from best to worst was DOPM, MEPM, IC, BAPM, ICRB, and TGC.

Sensitivity analyses with studies with Low risk of selection bias for concealment and excluding studies with small sample size were showed similar results and presented in the Figure S4

Table 1

Characteristics of included studies.

Author/Year	Age category	Study Design	Country	TOC (day)	Site of infection	APACHE II scores	Treatment	n
Babinchak 2005	A	Double-blind RCT	Europe, South Africa, and Asia	12–42	Appendicitis, cholecystitis, diverticulitis or colon.	Median: 6.0	Imipenem/cilastatin 500 mg/ 500 mg × 4	1759
						Median: 6.3	Tigecycline initial 100 mg × 2, followed by 50 mg × 2	
Basoli 1997	A	Open RCT	Italy	7–10	Peritonitis, appendicitis, biliary tract, bowel or stomach.	≤10: 80.2%	Imipenem/cilastatin 0.5 g × 3	287
						≤10: 85.0%	Meropenem 1 g × 3	
Brismar 1995	A	Open RCT	Sweden	7–14 and 28–42	Appendicitis, perforated peptic ulcer, perforation of small intestine, colonic perforation, biliary tract infection or gynaecological infections.	≤10: 89.7%	Imipenem/cilastatin 0.5 g/ 0.5 g × 3	249
						≤10: 90.9%	Meropenem 0.5 g × 3	
Brismar 1996	A	Open RCT	Sweden	7–14 and 28–42	Appendicitis, perforated peptic ulcer, perforation of small intestine, colonic perforation, complicated cholecystitis, pancreatitis or gynaecologic infections.	≤10: 90.0%	Imipenem/cilastatin 0.5 g/ 0.5 g × 4	118
						≤10: 93.1%	Biapenem 0.5 g × 3	
Cannavino 2015	C	Double-blind RCT	NR	7–14	NR	NR	Doripenem 20 mg/kg × 3 meropenem 20 mg/kg × 3	41
Chen 2010	A	Open RCT	China	12–37	Appendicitis, perforated diverticulitis, complicated cholecystitis, purulent peritonitis or peritonitis.	Mean ± SD: 4.1 ± 2.7	Imipenem/cilastatin 0.5 g × 4	203
						Mean ± SD: 5.1 ± 3.9	Tigecycline 0.1 g × 2	
Chen 2018	A	Double-blind RCT	China	14 and 21	Appendicitis, peritonitis, perforated stomach, complicated cholecystitis, peritonitis due to perforation of large intestinea, liver abscess, intra-abdominal abscess and complicated diverticulitis.	≤15: 100.0%	Imipenem/cilastatin 0.5 g/ 0.5 g × 4	470
						≤15: 100.0%	Tigecycline 0.1 g × 2	
Fomin 2005	A	Double-blind RCT	Europe, South Africa, Australia, and Asia	14–35	Appendicitis, cholecystitis, diverticulitis, intra-abdominal abscess, peritonitis or gastric.	Median: 6.41	Imipenem/cilastatin 0.5 g/ 0.5 g × 4	861
						Median: 6.44	Tigecycline initial 100 mg × 2 followed by 50 mg × 2	
Fomin 2008	A	Double-blind RCT	European	12–44	Appendicitis, cholecystitis or intra-abdominal abscess.	NR	Imipenem/cilastatin 0.5 g/ 0.5 g × 4	607
							Tigecycline initial 100-mg × 2 followed by 50 mg × 2	
Geroulanos 1995	A	Open RCT	European	14–28	Appendix, stomach, bilary tract or liver, cholecystitis, cholangitis, pancreas, small or large bowel.	NR	Imipenem/cilastatin 0.5 g/ 0.5 g × 3	232
							Meropenem 1 g × 3	

(*continued*)

Table 1
(continued).

Author/Year	Age category	Study Design	Country	TOC (day)	Site of infection	APACHE II scores	Treatment	n
Kanellakopoulou 1993	A	Open RCT	Greece	within 30	Appendicitis, duodenal or gastric ulcer perforation, gallbladder cmpyema and cholecystitis, choleperitoneum, sigmoid perforation, ischemic intestinal necrosis, purulent salpingitis, pyometra or torsion of ovarian cyst.	NR	Meropenem 1 g × 3	62
Lucasti 2008	A	Double-blind RCT	United States, Argentina, Brazil, Germany, Poland and Canada	21-60	Appendix, colon, biliary/cholecystitis, small bowel, stomach/duodenum or parenchymal/liver.	≤10: 90.8%	Imipenem/cilastatin 1 g × 3 Doripenem 0.5 g × 3	476
Lucasti 2016	A	Double-blind RCT	USA	5–9	Appendicitis, diverticular abscess, cholecystitis, stomach/duodenum/ jejunum/ileum/colon perforated or intra-abdominal abscess.	≤10: 91.7% ≤15: 95.3%	Meropenem 1 g × 3 Imipenem/cilastatin 0.5g × 4	385
						≤15: 96.4%	Imipenem/cilastatin 0.5g × 4 + relebactam 250 mg × 4	
						≤15: 96.6%	Imipenem/cilastatin 0.5g × 4 + relebactam 250 mg 125 mg × 4	
Oliva 2005	A	Double-blind RCT	United States, Canada, Europe, Latin America, India, and Asia	14–35	Appendicitis, perforation of intestine, diverticulitis, intra-abdominal abscess, peritonitis, gastric/duodenal perforation or cholecystitis.	Median: 5.5	Imipenem/cilastatin 1 g × 4	834
						Median: 5.6	Tigecycline initial 100 mg × 2 followed by 50 mg × 2	
Zanetti 1999	A	Open RCT	Switzerland	14	Diverticulitis, appendicitis, colitis, cholecystitis, ileum or jejunum, rectum.	≤10: 89%	Meropenem 0.5 g × 3	161
						≤10: 86%	Imipenem/cilastatin 0.5 g × 4	

A = adult; APACHE = Acute Physiology and Chronic Health Evaluation; B = both adult and child; C = child; cIAI = complicated intra-abdominal infection; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; TOC = Test-of-Cure.

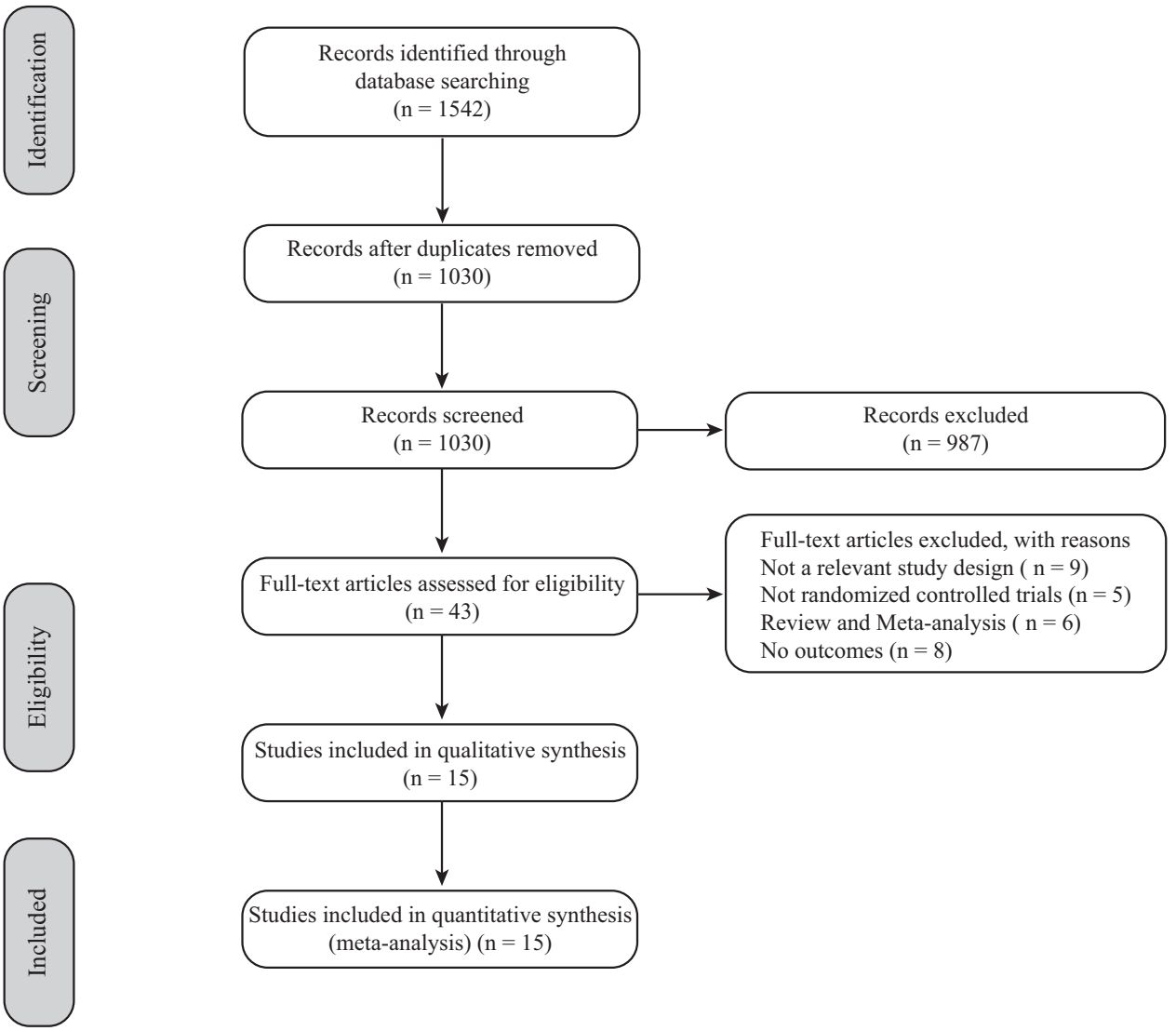

Figure 1. Selection process for the studies included in the meta-analysis.

(Supplemental Content Fig. S4, http://links.lww.com/MD/D266, which illustrates the forest plot of sensitivity analysis of microbiological treatment success by low risk of selection bias for concealment) and Figure S5 (Supplemental Content Fig. S5, http://links.lww.com/MD/D266, which illustrates the forest plot of sensitivity analysis of microbiological treatment success by excluding studies with small sample size).

3.6. Adverse events (AEs)

Fifteen studies including 6607 patients had experienced AEs. This analysis revealed no significant difference among most of comparison. In traditional meta-analysis, TGC showed higher risk of AEs compared with IC (OR = 1.53, 95% CrI = 1.02–2.41, see Supplemental Fig. S6, http://links.lww.com/MD/D266, which illustrates the forest plot of AEs).

As a result, SUCRA plot was showed in Fig. S7 (Supplemental Content Fig. S7, http://links.lww.com/MD/D266, which illustrates the SUCRA and rank probability for AEs) and indicated that risk of AEs from lower to higher was MEPM, IC, BAPM, DOPM, ICRB, and TGC.

3.7. Mortality

Mortality was reported in ten trials including 5359 patients. No mortality differences were noted between those treated with carbapenems vs those treated with different carbapenems or TGC according to meta-analysis (see Supplemental Fig. S8, http://links.lww.com/MD/D266, which illustrates the forest plot of mortality).

As a result, SUCRA plot was showed in Figure S9 (Supplemental Content, http://links.lww.com/MD/D266, which illustrates the SUCRA and rank probability for mortality) and indicated that risk of mortality from lower to higher was BAPM, DOPM, MEPM, IC, TGC, and ICRB.

4. Discussion

In the present study, we systematically reviewed all published RCTs comparing different carbapenems based regimen vs TGC for the treatment of patients with cIAIs. The results of the primary outcomes showed no difference in the clinical and microbiological treatment success and risk of AEs and mortality among cIAIs patients treated with either a carbapenem or TGC. Along with the

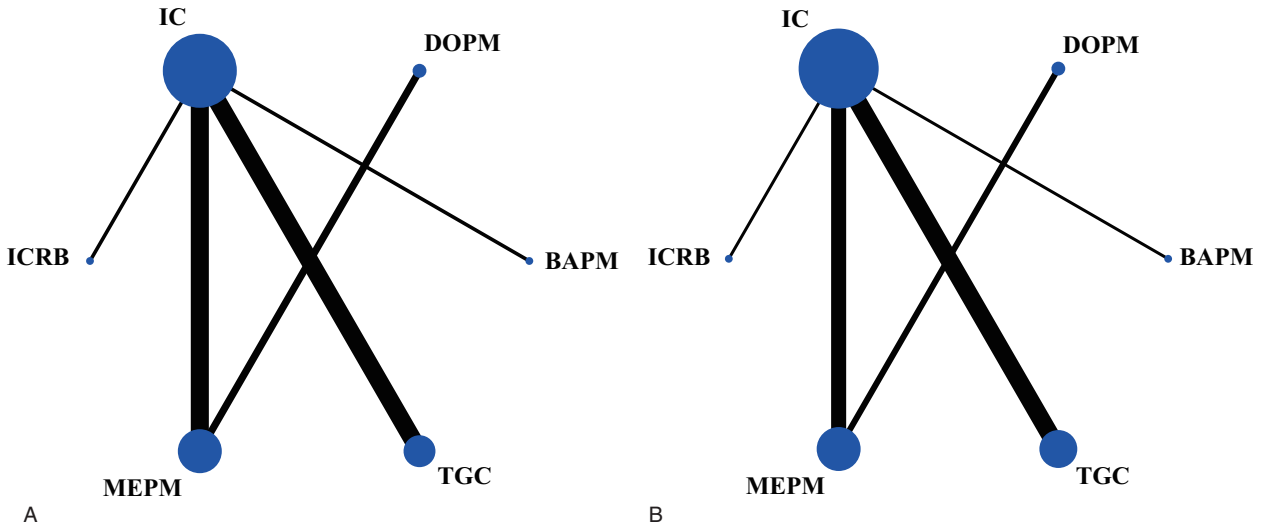

Figure 2. Network plot for clinical and microbiological treatment success. (A) clinical treatment success; (B) microbiological treatment success. BAPM = biapenem, DOPM = doripenem, IC = imipenem/cilastatin, ICRB = imipenem/cilastatin/relebactam, MEPM = meropenem, TGC = tigecycline.

development of carbapenem-resistant *Enterobacteriaceae* including *Klebsiella* spp. and *E coli*, in particular, has increased dramatically in the last decade. The use of carbapenems should be limited so as to preserve activity of this class of antibiotics because of the concern of emerging carbapenem-resistance.[12] However, due to the lack of direct comparisons of different carbapenems or TGC, physicians were still confused in the choice of a better treatment method. Hence, this network meta-analysis was performed to solve the dilemma. We believe this is the first network meta-analysis and evaluate clinical and microbiological outcomes in carbapenems and TGC. As MICs, pharmacokinetics and causative organisms were not available in the meta-analyses, we cannot comment on how this should impact treatment decisions.

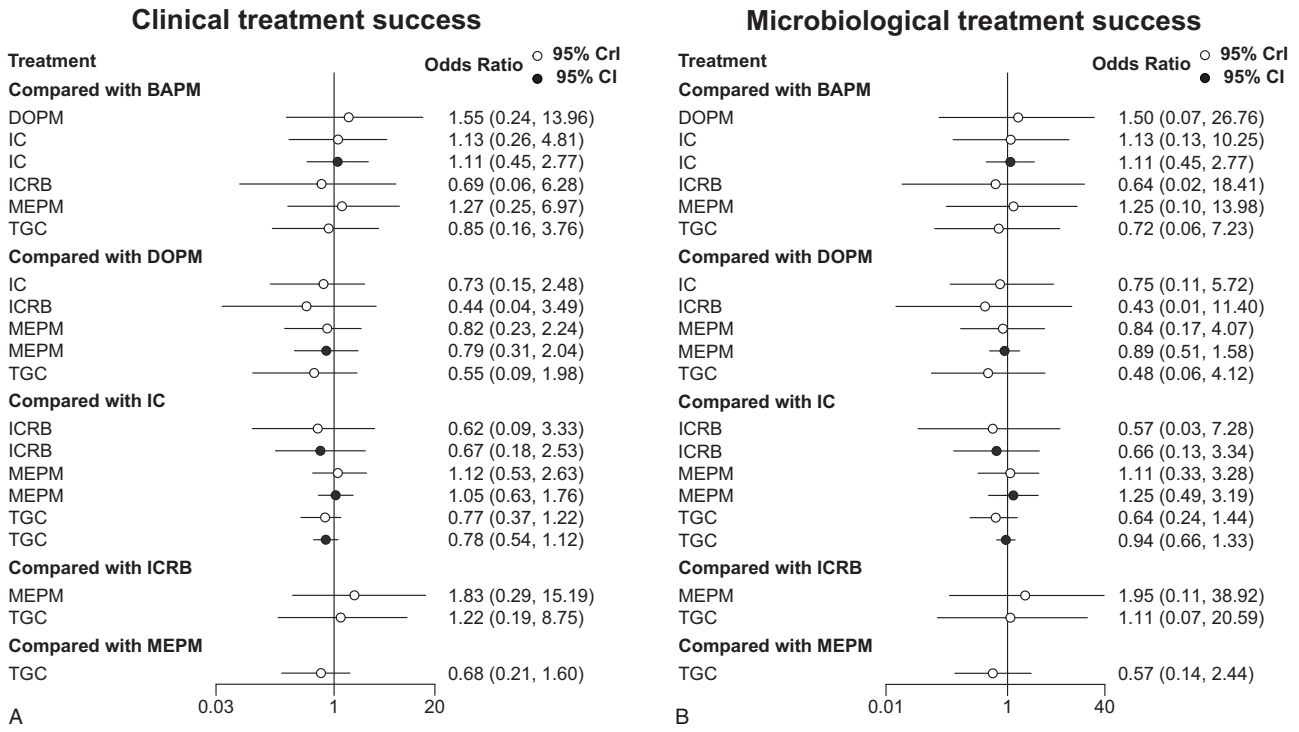

Figure 3. Forest plot from both the Bayesian network meta-analysis (open circle; CrI, credible intervals) and traditional meta-analysis (solid circle; CI, credible interval) for clinical and microbiological treatment success. (A) clinical treatment success; (B) microbiological treatment success. BAPM = biapenem; DOPM = doripenem; IC = imipenem/cilastatin; ICRB = imipenem/cilastatin/relebactam; MEPM = meropenem; TGC = tigecycline.

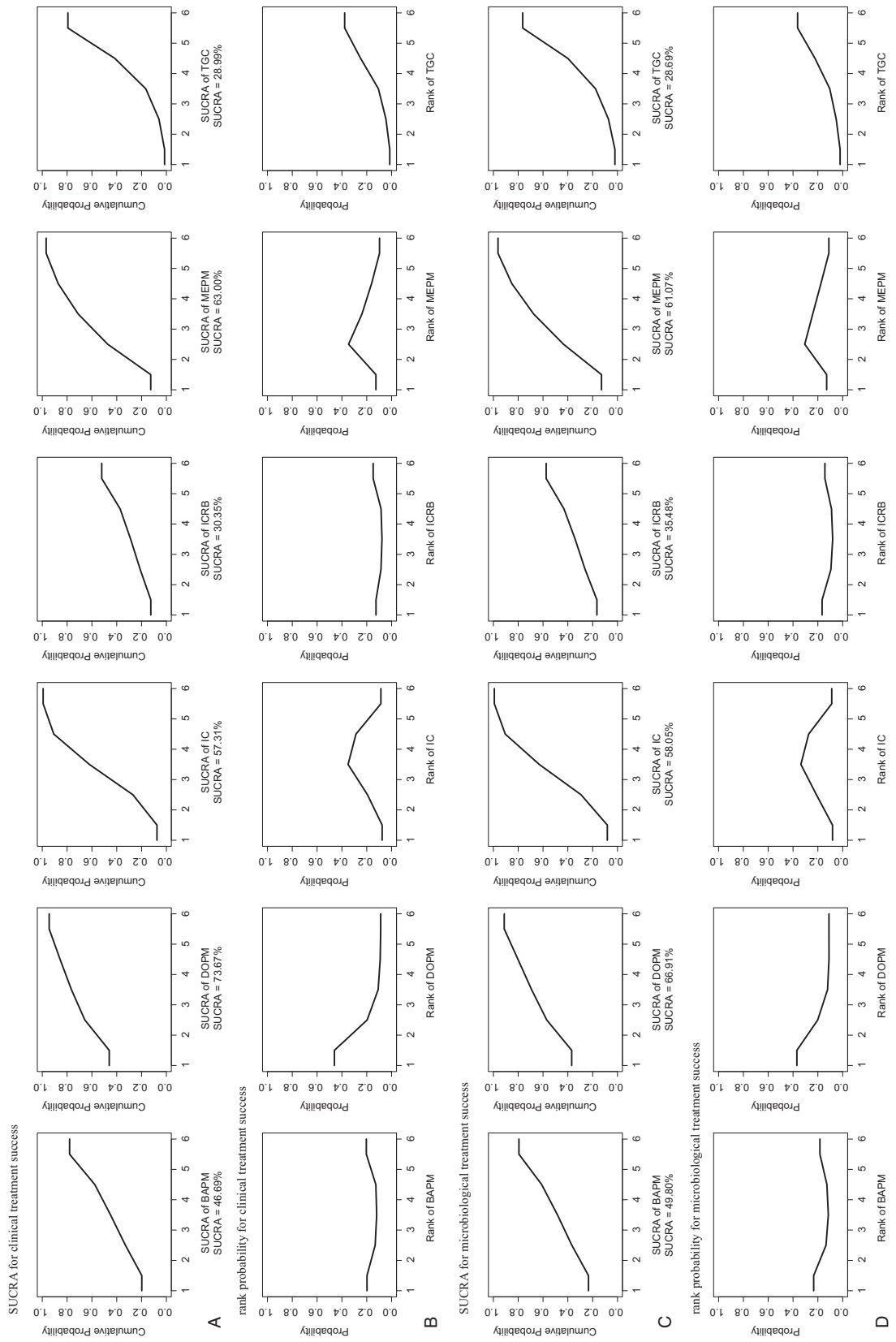

Figure 4. SUCRA and rank probability for clinical and microbiological treatment success. (A) SUCRA for clinical treatment success; (B) rank probability for clinical treatment success; (C) SUCRA for microbiological treatment success; (D) rank probability for microbiological treatment success. BAPM = biapenem, DOPM = doripenem, IC = imipenem/cilastatin, ICRB = imipenem/cilastatin/relebactam, MEPM = meropenem, SUCRA = the surface under the cumulative ranking curve, TGC = tigecycline.

Antimicrobial therapy for cIAIs is prescribed empirically. Recently, the Surgical Infection Society and Infectious Diseases Society of America, the World Society of Emergency Surgery published guidelines on this issue, suggesting that carbapenems offer a wide spectrum of antimicrobial activity against Gram-positive and Gram-negative aerobic and anaerobic pathogens.[4,12,13] On the other hand, TGC is a viable treatment choice, especially for cIAIs empiric therapy, due to its favorable in vitro activity against anaerobic organisms, enterococci, several ESBL- and in association carbapenems-producing *Enterobacteriaceae*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*.[12] The choice of therapy is physician oriented and is based on the local bacterial epidemiology, the infection site, acquisition (community acquired, health care associated or hospital acquired) and risk for treatment failure and death.[45]

The study has several key findings. First, there is no difference in the clinical and microbiological treatment success and risk of AEs and mortality among cIAIs patients treated with either a carbapenem or TGC. Second, according to the results of probabilities of rankings and SUCRAs, DOPM had the best performance in the clinical and microbiological treatment success with lesser AEs. Finally, TGC was related to higher rates of clinical and microbiological failure and higher risk AEs. The increased risk of failure observed in patients treated with TGC may be because of limitation of articles publication and TGC was only compared with IC. On the other hand, ICRB as a novel β-lactamase inhibitor combination, was also related to higher rates of clinical and microbiological failure and higher risk AEs. However, the result was imprecise due to only one studies evaluated ICRB compared with IC.

Balancing the evidence for drug efficacy and side effects, DOPM appears to be the best available treatment for cIAIs. Therefore, it is reasonable to consider that DOPM is one of the best carbapenem monotherapy for cIAIs. MEPM and IC was also associated with higher rates of clinical and microbiological treatment success following DOPM. As for safety, MEPM and BAPM was related to low risk of AEs and mortality. Empiric antimicrobial treatment of patients with cIAIs should be selected in light of the local bacterial epidemiology and patterns of resistance.

Overall, the quality of RCTs was moderate. The present study during the meta-analysis is subject to several limitations. First, MICs and pharmacokinetic data of antibacterial agents were not reported for the studies, which may impair the generalizability of our findings. Second, intra-abdominal infections encompass a wide range of spectrum of infection diseases with different bacterial species depending on the source, such as gastroduodenal vs peritonitis vs appendix vs colon, it is possible that certain antimicrobials perform better for colon infections and worse for other infections, but cumulatively they appear equal. In addition, variables including age, sex, underlying disease, and nutritional status of patients were also the potential bias-inducing factors. Third, definitions of cIAIs and clinical and microbiological treatment success were not completely consistent among studies; source control is of paramount importance in patients with cIAIs and is difficult to standardize.[46] Hence, this study used the primary outcome of clinical and microbiological treatment success to reduce the likelihood of misclassification bias, but the identified studies used different definitions of "clinical and microbiological treatment success". Last but not least, the non-blinding study design may have leaded to performance and detection biases. In addition, some regimen of carbapenems were not included in our studies, such as ertapenem, due to those RCT not meeting inclusion criteria, and well-conducted RCTs are urgently needed. Extrapolation of our findings in this population should be performed with caution.

5. Conclusions

In conclusion, the current meta-analysis revealed that different carbapenems can be an effective and safe treatment option for cIAI, similar to TGC. Balancing the evidence for drug efficacy and side effects, DOPM appears to be the best available treatment for cIAIs, according to the results of probabilities of rankings and SUCRAs. Therefore, it is reasonable to consider that DOPM is one of the best carbapenem monotherapy for cIAIs. MEPM and IC was also associated with higher rates of clinical and microbiological treatment success following DOPM. Empiric antimicrobial treatment of patients with cIAIs should be selected in light of the local bacterial epidemiology and patterns of resistance. Further study is required to determine whether carbapenems or TGC compared with other alternatives antibacterial agents, such as β-lactams combined therapy with metronidazole. Research may focus on patients with healthcare-associated cIAIs and the critically ill, and clinical outcomes should ideally be stratified by infection site, such as appendicitis.

Author contributions

Conceptualization: Lingyuan Chen, Xueyan Liang.
Data curation: Lingyuan Chen, Xueyan Liang.
Formal analysis: Xianshu Li, Yan Li.
Funding acquisition: Lingyuan Chen.
Investigation: Lingyuan Chen, Xueyan Liang, Junsong Jiang.
Methodology: Yan Li.
Project administration: Lingyuan Chen, Xianshu Li.
Software: Lingyuan Chen, Xueyan Liang, Yan Li.
Supervision: Junsong Jiang.
Validation: Yan Li.
Writing – original draft: Lingyuan Chen.
Writing – review & editing: Xueyan Liang, Yan Li.

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