Systematic Review and Meta-Analysis

Medicine®

OPEN

Carbapenems versus alternative β-lactams monotherapy or in combination for febrile neutropenia

Systematic review and meta-analysis of randomized controlled trial

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

Abstract

Background: Febrile neutropenia (FN) in cancer patients can be life threatening and require the timely antimicrobial agents treatment.

Methods: To compare the effectiveness and safety of carbapenems versus β-lactams for FN. PubMed, Medline (Ovid SP), Cochrane CENTRAL, and Embase were searched up to March 2019. FN in patients due to undergoing chemotherapy and treated with carbapenems and β-lactams were included. Odds ratio (OR) and 95% confidence interval (CI) were estimated.

Results: Fifty randomized controlled trials (RCTs) studies involving 10,995 participants were included. Carbapenems were more likely to experience treatment success without modification (OR = 1.34, 95% CI = 1.24–1.46) compared with β-lactams. Meropenem (OR = 1.36, 95% CI = 1.18–1.56; OR = 1.24, 95% CI = 1.01–1.53), imipenem/cilastatin (OR = 1.40, 95% CI = 1.19–1.65; OR = 1.31, 95% CI = 1.04–1.67) showed higher effectiveness from that by β-lactams monotherapy or in combination with aminoglycoside, respectively. Carbapenems–aminoglycoside combination therapy does not provide an advantage over carbapenems alone. Meropenem showed similar risk of adverse events (AEs) versus β-lactams. Imipenem/cilastatin was related to higher risk of AEs compared with β-lactams. There was no significant difference between carbapenems and β-lactams monotherapy or in combination.

Conclusion: Meropenem and imipenem/cilastatin monotherapy appears to be available treatment for FN compared with β-lactams. Imipenem/cilastatin was related to higher risk of AEs. Balancing the evidence for drug efficacy and side effects, meropenem monotherapy appears to be available treatment for FN. Individual centers should select the best matching therapy regimens according to local epidemiology and susceptibility patterns.

Abbreviations: AEs = adverse events, CI = confidential interval, FN = febrile neutropenia, OR = odds ratio, RCT = randomized controlled trial.

Keywords: β-lactams, carbapenems, febrile neutropenia, meta-analysis, systematic review

Editor: Mehmet Bakir.

XGT and LYC contributed equally to this work.

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

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are publicly available.

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

[*] Correspondence: Xueyan Liang, The People's Hospital of Hechi, Hechi, Guangxi, China (e-mail: liangxueyan20102010@outlook.com).

How to cite this article: Tang X, Chen L, Li Y, Jiang J, Li X, Liang X. Carbapenems versus alternative β-lactams monotherapy or in combination for febrile neutropenia: Systematic review and meta-analysis of randomized controlled trial. Medicine 2020;99:43(e22725).

Received: 26 December 2019 / Received in final form: 14 July 2020 / Accepted: 15 September 2020

http://dx.doi.org/10.1097/MD.0000000000022725

1. Introduction

Febrile neutropenia (FN) remains a frequent complication of chemotherapy for patients with cancer, particularly among patients with hematologic malignancies, can be life threatening and require prompt immediate medical attention for evaluation and administration of broad-spectrum antimicrobial agents empirically.[1] In cancer patients, FN is associated with considerable morbidity, mortality, and increased medical cost.[2] Epidemiologic surveys have shown that ~40% to 60% of these infections are caused by gram positive organisms, ~20% to 25% by gram-negative organisms, and ~20% to 25% are polymicrobial.[3–5]

Consequently, in the clinical guideline for the use of antimicrobial agents in neutropenic patients with cancer, monotherapy with broad-spectrum antimicrobial agents, such as a carbapenem, cefepime, piperacillin/tazobactam or in combination with agents such as the aminoglycosides or vancomycin, is recommended in specific situations of complications or resistance as first-line therapy by the Infectious Diseases Society of America (IDSA),[6] and the National Comprehensive Cancer Network (NCCN).[7]

Carbapenems have been proven to have wider spectrum against bacteria in comparison with the available penicillin, cephalosporin, and β-lactam/β-lactamase inhibitor combinations. In general, carbapenems having different antibacterial activity such as imipenem, panipenem, and doripenem were effective against gram-positive bacteria, while meropenem, biapenem, ertapenem, and doripenem were a little bit effective against gram-negative organisms.[8] However, carbapenem-resistant *Enterobacteriaceae* including *Klebsiella* species and *Escherichia coli*, in particular, has increased dramatically in the last decade,[9] they are difficult to treat and associated with high mortality rates.

Although carbapenems have documented clinical and microbiologically efficacy in the treatment of FN, it is unclear if this effect is consistent across the range of published studies. With the widespread antibiotic resistance and few novel antibiotic agents on the horizon, it is paramount we understand the efficacy of individual antimicrobial classes. Due to the current lack of new antibiotic agents with dissemination mechanisms of resistance, appropriate use of these broad-spectrum agents for treatment of antimicrobial resistant gram-negative infections is critical needed to preserve their future utility. The main aim of the current study is to compare the effectiveness and safety of carbapenem versus alternative β-lactam monotherapy or in combination for FN patients. For this purpose, we assessed treatment success without antibiotics modification as the primary outcome. All adverse events (AEs), mortality, and superinfection were also assessed as the secondary outcomes.

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 for all publications from inception up to March 2019 were systematically searched. The following search terms were used: "febrile neutropenia" combined with "carbapenem," "imipenem," "meropenem," "biapenem," "ertapenem," "doripenem," "faropenem," "panipenem," "razupenem," "tebipenem," "tomopenem," or "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 enrollment studies.

2.2. Inclusion criteria

Studies meeting the following criteria were included: population: febrile cancer patients with neutropenia, induced by chemotherapy or bone marrow transplantation; intervention: FN patients treatment with carbapenems monotherapy or in combination; comparison: FN patients treatment with non-carbapenem β-lactams monotherapy or in combination; outcome: primary outcomes: treatment success without modification; secondary outcomes: all AEs; all-cause mortality, and infection-related mortality; superinfection; design: randomized controlled trials (RCTs).

2.3. Exclusion criteria

The exclusion criteria were reviews, non-clinical studies and case observations; not RCTs; reduplicated studies; not accepted granulocyte transfusion; improper outcome measures; meta-analysis, case reports, and editorials.

2.4. Selection of studies and data extraction

Comprehensive search of databases were performed by 2 researchers (XT and LC), 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, cancer type interventions, comparisons, and outcomes.

2.5. Risk of bias assessment

Three reviewers (XT, LC, and XL) independently evaluated the methodological quality of identified studies. The "risk of bias tool" from the Cochrane Handbook for Systematic Reviews of Interventions version 5.3.0 was used to assess methodological quality.[10,11] In terms of the assessment criteria, each study was evaluated and assessed to 1 of the 3 following risk of bias: "low risk of bias" (+), "unclear risk of bias" (?), and "high risk of bias" (–).[11]

2.6. Data analysis

Data were analyzed using the Review Manager 5.3.0. software (The Nordic Cochrane Centre, Copenhagen, Denmark). Dichotomous outcomes were expressed as odds ratio (OR) with 95% confidence intervals (CI). Test of heterogeneity was conducted with the I^2 test and Q statistic which is distributed as a Chi-squared variate under the assumption of homogeneity of effect sizes.[12] A value of $I^2 > 50\%$ or $P < .05$ was assumed to indicate significant heterogeneity. Publication/reporting biases were visually assessed using funnel plots. If there was no observed heterogeneity, the fixed-effect model was chosen.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess confidence in estimates of effect associated with specific drug comparisons was

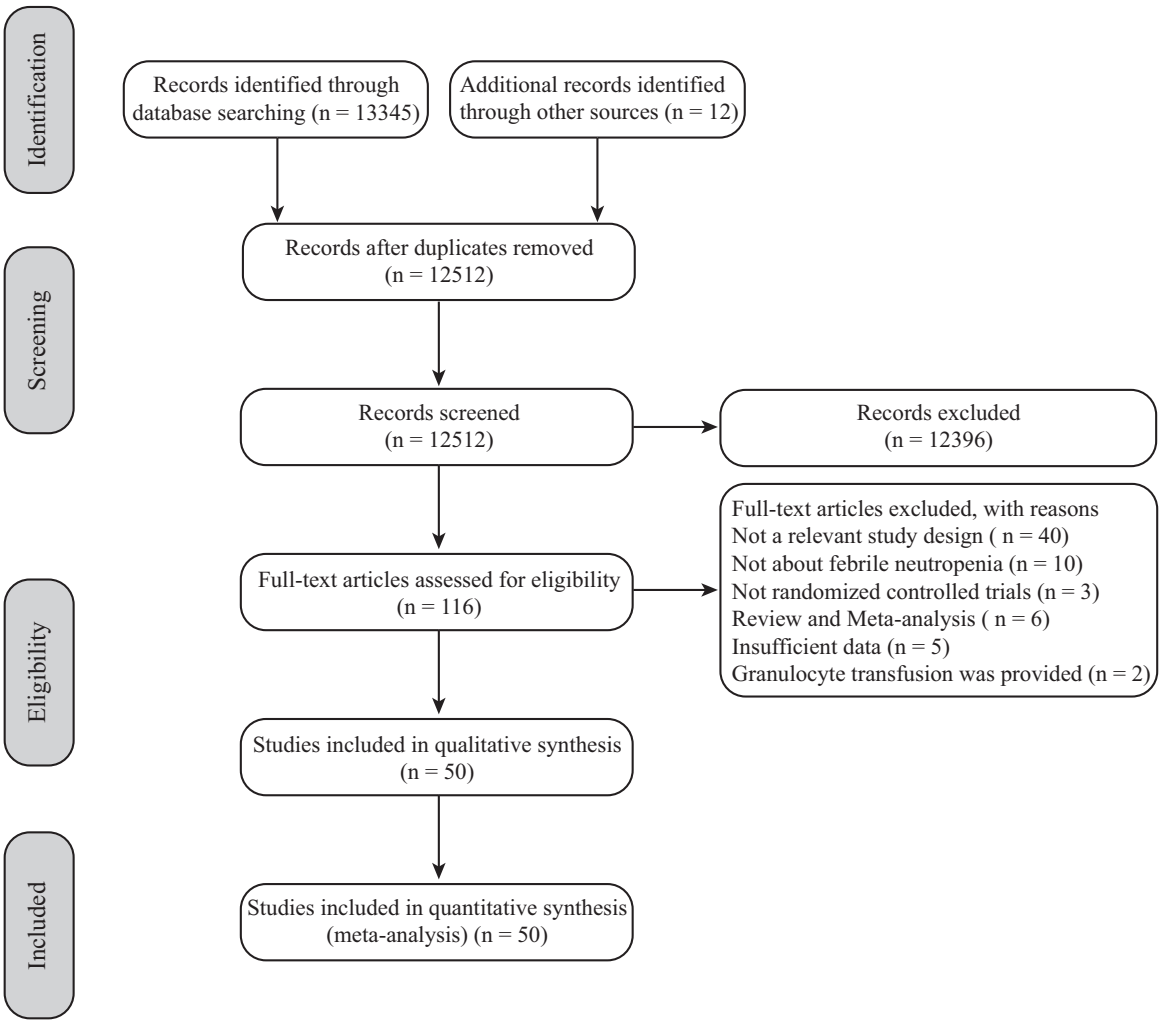

Figure 1. Selection process for the studies included in the meta-analysis.

used to determine confidence in the evidence for treatment success without modification, all AEs, and mortality. Sensitivity analysis was based on: analyzing studies with low risk of selection bias due to sequence generation and concealment. Excluding studies that did not clearly define assessment of treatment success without modification. Excluding studies that did not clearly define the FN. Excluding studies with small sample size (at the 25th percentile).[13,14] To determine whether the results were affected by study characteristics, we performed subgroup meta-analysis on primary outcomes according to the separate evaluation of patients with microbiologically defined infection, microbiologically not proven but clinically defined infection, and fever of unknown origin,[15,16] subgroups of trials limited to pediatric cases and adult cases, subgroups of trials limited to hematological malignancy.

3. Results

3.1. Study identification and selection

A total of 13,345 records were retrieved from the initial database search. After removing 833 duplicate articles, 12,512 records were eligible. Based on the inclusion and exclusion criteria, 12,396 articles were excluded after a simple reading of the titles and abstracts of the articles. The remaining 116 full-text articles were assessed for eligibility. Furthermore, not a relevant study design, not RCT, meta-analysis, reported insufficient data were excluded. Finally, a total of 50 RCTs studies were included in the meta-analysis (Supplemental Content Table S1, http://links.lww.com/MD/F34 and Appendix 1, http://links.lww.com/MD/F18, Table S1, http://links.lww.com/MD/F34 illustrates the characteristics of included studies and Appendix 1 list the included randomized controlled trials). The selection process is shown in Fig. 1.

3.2. Study characteristics

The basic characteristics of the included studies are listed in Table 1. Fifty RCTs studies involving 10,995 participants were included in the analysis. These studies were published from 1987 to 2017. The number of participants in the studies ranged from 28 to 1034. The definitions of FN and observation durations for outcomes were summarized in the Supplemental Content Table S2, http://links.lww.com/MD/F35 and Table S3, http://links.lww.com/MD/F36 (Table S2, http://links.lww.com/MD/F35 illustrates the definitions of febrile neutropenia and

Table 1

Summary of confidence of findings (GRADE).

Outcome	Effect estimate OR (95% CI)*	Number of participants (studies)	Quality of the evidence (GRADE)†
Meropenem versus β-lactams			
Treatment success without modification	1.36 (1.18, 1.56)	3518 (16)	●●●○ Moderate‡
Microbiologically documented infections	1.15 (0.79, 1.66)	515 (7)	●●●○ Moderate‡
Fever of unknown origins	1.60 (1.22, 2.09)	944 (8)	●●●○ Moderate‡
Clinically documented infections	1.35 (0.83, 2.20)	282 (7)	●●●○ Moderate‡
Adverse events	1.05 (0.78, 1.42)	1883 (9)	●●●○ Moderate‡
All-cause mortality	0.77 (0.42, 1.39)	1614 (6)	●●●○ Moderate‡
Infection-related mortality	0.80 (0.38, 1.69)	1595 (5)	●●●○ Moderate‡
Meropenem versus β-lactams combination with aminoglycoside			
Treatment success without modification	1.24 (1.01, 1.53)	1502 (8)	●●●○ Moderate‡
Microbiologically documented infections	1.17 (0.37, 3.74)	301 (3)	●●●○ Moderate‡
Fever of unknown origins	1.14 (0.78, 1.64)	505 (3)	●●●○ Moderate‡
Clinically documented infections	1.02 (0.63, 1.66)	274 (3)	●●●○ Moderate‡
Adverse events	0.96 (0.76, 1.21)	1503 (7)	●●●○ Moderate‡
All-cause mortality	0.92 (0.55, 1.55)	1165 (4)	●●●○ Moderate‡
Infection-related mortality	0.66 (0.29, 1.47)	1122 (3)	●●●● High
Meropenem combination with aminoglycoside versus β-lactam combination with aminoglycoside			
Treatment success without modification	1.31 (0.64, 2.69)	139 (2)	●●○○ Low§
Adverse events	1.11 (0.34, 3.67)	89 (1)	●●○○ Low§
All-cause mortality	1.53 (0.32, 7.32)	89 (1)	●●○○ Low§
Infection-related mortality	0.53 (0.09, 3.00)	139 (2)	●●○○ Low§
Panipenem versus β-lactams			
Treatment success without modification	0.86 (0.49, 1.52)	282 (2)	●●○○ Low§
Microbiologically documented infections	0.72 (0.20, 2.63)	40 (2)	●●○○ Low§
Fever of unknown origins	0.93 (0.41, 2.08)	171 (2)	●●○○ Low§
Clinically documented infections	0.81 (0.11, 6.04)	61 (2)	●○○○ Very low‖
Adverse events	1.13 (0.54, 2.32)	282 (2)	●●○○ Low§
All-cause mortality	1.37 (0.39, 4.77)	116 (1)	●●○○ Low§
Infection-related mortality	1.11 (0.07, 18.20)	116 (1)	●●○○ Low§
Imipenem versus β-lactams			
Treatment success without modification	1.40 (1.19, 1.65)	2733 (11)	●●○○ Low¶
Microbiologically documented infections	1.43 (0.91, 2.27)	294 (4)	●○○○ Very low‖
Fever of unknown origins	0.89 (0.64, 1.24)	788 (6)	●●●○ Moderate‡
Clinically documented infections	1.12 (0.46, 2.72)	93 (4)	●●●○ Moderate‡
Adverse events	1.73 (1.37, 2.19)	2036 (7)	●○○○ Very low‖
All-cause mortality	0.61 (0.29, 1.27)	1130 (6)	●●●○ Moderate‡
Infection-related mortality	2.10 (0.19, 23.39)	399 (1)	●●○○ Low§
Imipenem versus β-lactams combination with vancomycin			
Treatment success without modification	3.20 (1.21, 8.47)	89 (1)	●○○○ Very low#
Imipenem combination with vancomycin versus β-lactams combination with vancomycin			
Treatment success without modification	0.95 (0.59, 1.50)	369 (1)	●○○○ Very low#
Microbiologically documented infections	0.86 (0.24, 3.06)	84 (1)	●○○○ Very low#
Fever of unknown origins	0.83 (0.45, 1.52)	217 (1)	●●○○ Low**
Clinically documented infections	1.21 (0.46, 3.21)	68 (1)	●●○○ Low**
Adverse events	2.24 (1.10, 4.58)	452 (1)	●●○○ Low**
Imipenem versus β-lactams combination with aminoglycoside			
Treatment success without modification	1.31 (1.04, 1.67)	1356 (10)	●●●○ Moderate‡
Microbiologically documented infections	1.77 (1.13, 2.75)	407 (5)	●●●○ Moderate‡
Fever of unknown origins	1.44 (1.03, 2.00)	750 (6)	●●●○ Moderate‡
Clinically documented infections	1.71 (0.89, 3.26)	193 (5)	●●●○ Moderate‡
Adverse events	0.80 (0.60, 1.06)	1354 (8)	●●○○ Low**
All-cause mortality	0.33 (0.09, 1.16)	227 (2)	●●○○ Low**
Infection-related mortality	0.66 (0.25, 1.71)	489 (4)	●●○○ Low§
Imipenem combination with aminoglycoside versus β-lactams			
Treatment success without modification	2.22 (1.41, 3.50)	357 (1)	●○○○ Very low#
Fever of unknown origins	5.32 (2.67, 10.58)	184 (1)	●○○○ Very low#
Adverse events	2.49 (1.05, 5.89)	357 (1)	●○○○ Very low#
Imipenem combination with aminoglycoside versus β-lactams combination with aminoglycoside			
Treatment success without modification	1.32 (0.86, 2.02)	441 (2)	●●○○ Low§
Microbiologically documented infections	3.11 (0.41, 23.39)	17 (1)	●○○○ Very low#
Fever of unknown origins	1.59 (0.83, 3.04)	244 (2)	●●○○ Low**

(*continued*)

Table 1

(continued).

Outcome	Effect estimate OR (95% CI)*	Number of participants (studies)	Quality of the evidence (GRADE)†
Clinically documented infections	3.00 (0.06, 151.19)	3 (1)	●○○○ Very low#
Adverse events	1.77 (0.83, 3.78)	372 (1)	●○○○ Very low

* Effects of specific carbapenems versus non-carbapenem β-lactams-based antibacterial agents on primary outcomes and secondary outcomes.

† GRADE Working Group grades of evidence. High quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate.

‡ Downgraded for study limitations (–1).

§ Downgraded for study limitations (–1) and imprecision (–1).

‖ Downgraded for study limitations (–1), inconsistency (–1), and imprecision (–1).

¶ Downgraded for study limitations (–1) and inconsistency (–1).

Downgraded for study limitations (–2) and imprecision (–1).

** Downgraded for study limitations (–2).

Table S3, http://links.lww.com/MD/F36 illustrates the observation durations for outcomes and definition of outcomes). The outcomes of risk of bias are summarized in Supplemental Content Figure S1, http://links.lww.com/MD/F19 (which illustrates the methodological quality assessment of the risk of bias for each included study). Eighteen studies described the randomization method. Three studies adopted double-blind design and 6 studies adopted single-blind design. For random sequence generation, allocation concealment, blinding, and incomplete outcome data, the majority of studies were judged as having high or unclear risk of bias. Most RCTs were at low risk for the reporting bias.

3.3. Overview

The exhaustive analyses describing comparisons between carbapenems-based antibacterial versus non-carbapenem β-lactams-based antibacterial agents were presented in detail in the related Supplementary material. Effects of specific carbapenems versus non-carbapenem β-lactams-based antibacterial agents on primary outcomes and secondary outcomes were showed in Fig. 2 and Supplemental Content Figure S2–S11 http://links.lww.com/MD/F20, http://links.lww.com/MD/F21, http://links.lww.com/MD/F22, http://links.lww.com/MD/F25, http://links.lww.com/MD/F24, http://links.lww.com/MD/F26, http://links.lww.com/MD/F27, http://links.lww.com/MD/F28, http://links.lww.com/MD/F29, http://links.lww.com/MD/F30, http://links.lww.com/MD/F31, http://links.lww.com/MD/F32, http://links.lww.com/MD/F33. The results of GRADE assessments for treatment success without modification, all AEs, and mortality based on specific carbapenems versus non-carbapenem β-lactams-based antibacterial agents were showed in Table 1.

3.4. Primary outcomes

3.4.1. Treatment success without modification. The results of treatment success without antibiotics modification were evaluated in 49 studies including 10,786 patients, of whom 6412 achieved treatment success.

Meta-analysis showed that patients treated with carbapenems-based antibacterial agents were more likely to experience treatment success without modification (OR = 1.34, 95% CI = 1.24–1.46, $I^2 = 31\%$, Fig. 2) compared with non-carbapenem β-lactams-based antibacterial agents.

Subgroup analyses based on specific antimicrobials mostly replicated the findings of the original analysis. Compared with β-lactams-based antibacterial agents monotherapy or in combination with aminoglycoside, treatment success rates by meropenem (OR = 1.36, 95% CI = 1.18–1.56, $I^2 = 38\%$; OR = 1.24, 95% CI = 1.01–1.53, $I^2 = 0\%$; Fig. 2, respectively), imipenem/cilastatin (OR = 1.40, 95% CI = 1.19–1.65, $I^2 = 50\%$; OR = 1.31, 95% CI = 1.04–1.67, $I^2 = 30\%$; Fig. 2, respectively) showed higher effectiveness for FN. The difference showed similar effectiveness of meropenem or imipenem/cilastatin combination with aminoglycoside versus β-lactam combination with aminoglycoside (OR = 1.31, 95% CI = 0.64–2.69, $I^2 = 0\%$; OR = 1.32, 95% CI = 0.86–2.02, $I^2 = 0\%$; Fig. 2, respectively), and panipenem/betamipron versus β-lactam monotherapy (OR = 0.86, 95% CI = 0.49–1.52, $I^2 = 0\%$, Fig. 2).

In subgroup analysis of microbiologically documented infection cases, fever of unknown origins cases, and clinically documented infections cases, similar results were observed of carbapenems-based trials (OR = 1.39, 95% CI = 1.13–1.71, $I^2 =$ 29%, Supplemental Content Figure S2, http://links.lww.com/MD/F20, which illustrates the treatment success of microbiologically documented infection cases; OR = 1.34, 95% CI = 1.16–1.54, $I^2 = 35\%$, Supplemental Content Figure S3, http://links.lww.com/MD/F21, which illustrates the treatment success of fever of unknown origins cases; OR = 1.33, 95% CI = 1.02–1.74, $I^2 = 0\%$; Supplemental Content Figure S4, http://links.lww.com/MD/F22 which illustrates the treatment success of clinically documented infections cases; respectively) versus β-lactams monotherapy or in combination.

In a subgroup analysis including studies only for adults, carbapenems was related to the higher treatment success rate compared with the other β-lactams (OR = 1.38, 95% CI = 1.25–1.52, $I^2 = 34\%$, Supplemental Content Figure S5, http://links.lww.com/MD/F25, which illustrates the treatment success including studies only for adults cases). Similar results were observed in a subgroup analysis including studies only for children (OR = 1.26, 95% CI = 1.04–1.54, $I^2 = 33\%$, Supplemental Content Figure S6, http://links.lww.com/MD/F24, which illustrates the treatment success including studies only for children cases). In a subgroup analysis including studies only for hematological malignancy, carbapenems had higher treatment success compared with other β-lactams. (OR = 1.34, 95% CI = 1.09–1.64, $I^2 = 39\%$, Supplemental Content Figure S7, http://links.lww.com/MD/F26, which illustrates the treatment success including studies only for hematological malignancy cases).

Similar results were observed in sensitivity analysis with studies with low risk of selection bias due to sequence generation and concealment (OR = 1.28, 95% CI = 1.11–1.49, $I^2 = 46\%$, Supplemental Content Figure S8, http://links.lww.com/MD/F27,

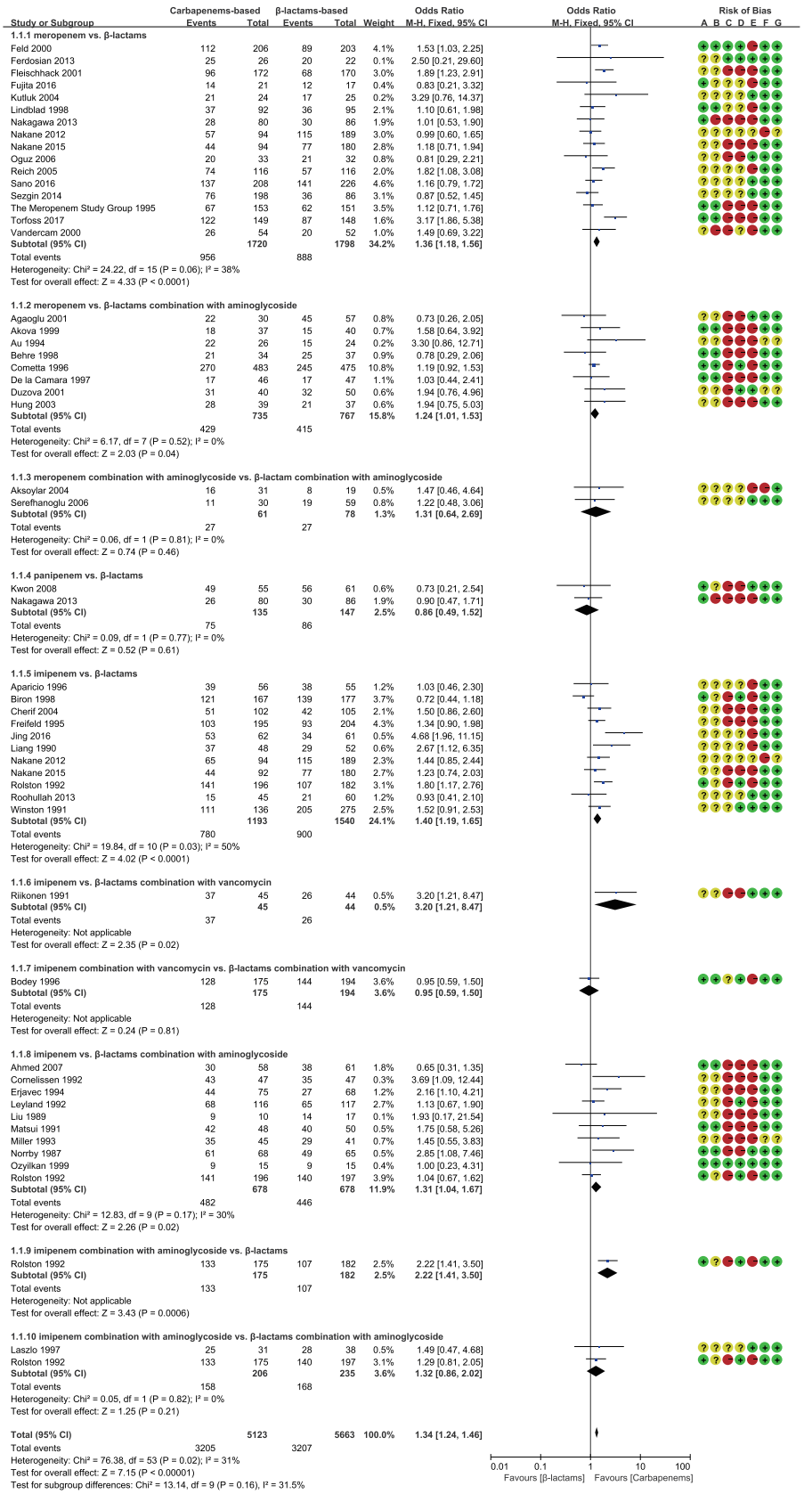

Figure 2. Forest plots of treatment success without modification. Risk of bias legend: (A), Random sequence generation (selection bias); (B), allocation concealment (selection bias); (C), blinding of participants and personal (performance bias); (D), blinding of outcome assessment (detection bias); (E), incomplete outcome data (attrition bias); (F), selective reporting (reporting bias); (G), other bias.

which illustrates the sensitivity analysis of studies with low risk of selection bias due to sequence generation or concealment), excluding studies that did not clearly define assessment of treatment success without modification (OR = 1.34, 95% CI = 1.23–1.46, I^2 = 36%, Supplemental Content Figure S9, http://links.lww.com/MD/F28, which illustrates the sensitivity analysis of excluding studies that did not clearly define assessment of treatment success without modification), excluding studies that did not clearly define the FN (OR = 1.31, 95% CI = 1.21–1.43, I^2 = 24%, Supplemental Content Figure S10, http://links.lww.com/MD/F29, which illustrates the sensitivity analysis of excluding studies that did not clearly define the FN), and excluding studies with small sample size (OR = 1.34, 95% CI = 1.24–1.46, I^2 = 40%, Supplemental Content Figure S11, http://links.lww.com/MD/F30, which illustrates the sensitivity analysis of excluding studies with small sample size).

3.5. Secondary outcomes

3.5.1. All AEs. The risks for all AEs were assessed in 33 RCTs consisting of 7453 subjects, of whom 1448 experienced any AEs. The results showed that patients treated with carbapenems were more likely to experience AEs (OR = 1.19, 95% CI = 1.05–1.34, I^2 = 50%, Supplemental Content Figure S12, http://links.lww.com/MD/F31, which illustrates the results of all AEs).

In subgroup analyses based on specific antimicrobials, patients treated with meropenem showed similar risk of AEs versus β-lactams, no matter monotherapy or in combination (OR = 1.05, 95% CI = 0.78–1.42, I^2 = 0%; OR = 0.96, 95% CI = 0.76–1.21, I^2 = 44%, Supplemental Content Figure S12, http://links.lww.com/MD/F31; respectively). However, imipenem/cilastatin was related to higher risk of AEs compared with β-lactams monotherapy (OR = 1.73, 95% CI = 1.37–2.19, I^2 = 0%, Supplemental Content Figure S12, http://links.lww.com/MD/F31).

3.5.2. All-cause mortality and infection-related mortality. The risk for all-cause mortality was assessed in 19 RCTs consisting of 4167 subjects, of whom 161 (3.86%) had died from any cause and 16 studies involving 3860 subjects observing the risk for infection-related mortality, of whom 80 (2.07%) had died from infection. Our study revealed that there was no significant difference between carbapenems and β-lactams monotherapy or in combination (Supplemental Content Figure S13, http://links.lww.com/MD/F32 and Figure S14, http://links.lww.com/MD/F33, Figure S13, http://links.lww.com/MD/F32 illustrates the results of all-cause mortality and Figure S14 illustrates the results of infection-related mortality).

4. Discussion

This systematic review and meta-analysis systematically and quantitatively evaluate the efficacy and safety of carbapenems-based monotherapy or in combination treatment compared with β-lactams-based antimicrobial agents for FN. A total of 50 studies from 22 countries were included. Data were collected from various geographic areas: 23 studies were conducted in Asia, 18 in Europe, 5 in North America, 2 in Europe and North America, 1 in Africa, and 1 in Oceania. Previous study was not investigated all carbapenems monotherapy, nor in compared with β-lactams-based antimicrobial agents for treatment of FN.

Previous systematic reviews and meta-analyses have argued that therapy in patients with FN has been published. Three studies published on the topic of empirical antibiotic monotherapy for FN,[17] anti-pseudomonal β-lactams for treatment of FN,[16] or β-lactams versus β-lactam-aminoglycoside combination therapy in cancer patients with neutropenia.[18] In those studies, only imipenem/cilastatin and meropenem or in combination were included and without panipenem/betamipron. One study on the topic of comparison of antipseudomonal β-lactams for FN empiric therapy without carbapenems or β-lactams in combination.[19] Besides, several new RCTs have been published. A systematic review and meta-analysis need to reflect current situation of medical research. Systematic reviews are necessary to update when new studies are published. Consequently, we performed a meta-analysis to evaluate the efficacy and safety of carbapenems monotherapy or in combination compared with β-lactams-based antimicrobial agents for FN.

The study has several key findings. First, meropenem or imipenem/cilastatin-based antimicrobial agents showed a higher treatment success rate compared with alternative β-lactams-based antimicrobial agents for FN. Sensitivity and subgroup analysis generally supported these findings. Second, carbapenems-aminoglycoside combination therapy does not provide an advantage over carbapenems alone. Third, patients treated with imipenem/cilastatin-based antimicrobial agents more likely to experience AEs. On the other hand, meropenem and panipenem/betamipron showed similar risk of AEs compared with β-lactams-based antimicrobial agents. Finally, carbapenems-based antimicrobial agents resulted in similar mortality versus β-lactams-based antimicrobial agents.

Balancing the evidence for drug efficacy and side effects, meropenem monotherapy appears to be available treatment for FN compared with β-lactams. Imipenem/cilastatin showed higher treatment success rate versus β-lactams, and it is a reasonable choice for FN empiric therapy. On the other hand, imipenem/cilastatin had the highest rate of AEs, and this result similar to previous meta-analyses.[17] However, previous meta-analyses revealed that imipenem/cilastatin was related to higher risk for AEs leading to discontinuation.[19] As for panipenem/betamipron, it was related to the poorest outcome for both treatment success in carbapenems. Although considering the limited power of included study, these results are not promising. Further research and high-quality RCTs are needed to confirm this finding.

Recent years have seen widespread antibacterial-resistance due to the increased use of antibiotics with a broad spectrum of antibacterial activity, exposure to antibiotics, frequent and/or long-term hospitalization, use of in-dwelling devices, and host factors provide risks for acquisition.[20] The emergence and subsequent dissemination of carbapenem-resistant gram-negative bacteria, especially plasmid-borne carbapenemases in *Enterobacteriaceae*, represent a global public health threat, continues to increase on a global level and is associated with significant morbidity and mortality.[21] Empiric antimicrobial treatment of patients with FN should be selected in light of the local bacterial epidemiology and patterns of resistance, bundled infection control measures, education and training, interventions aimed at healthcare-associated risk factors for colonization and/or infection.

The present study during the meta-analysis is subject to several limitations. First, the quality of RCTs was moderate, the biggest problem being non-blinding study design due to the different regimens being administered. Second, source control is of

paramount importance in patients with FN and is difficult to standardize. Also, the definitions of FN and treatment success were notably different across studies. Third, some unpublished article and missing data might lead bias to the pooled effect. Thus, the interpretation of our findings should be done with caution and high-quality RCTs are needed to confirm this finding. Finally, we were not estimate the impact that the different drugs could have on the global public health burden or the impact on the emerging problem of carbapenem resistance in neutropenic patients, resistance is likely promoted by previous carbapenem use and leads to high mortality rates.[22] Thus, individual centers should select the best matching therapy regimens according to local epidemiology and susceptibility patterns.

5. Conclusions

In sum, we carried out the systematic review and meta-analysis to compare efficacy and safety of carbapenems-based antimicrobial agents versus non-carbapenems β-lactams-based antimicrobial agents for FN. Meropenem and imipenem/cilastatin was related to the higher treatment success rate, however, imipenem/cilastatin was related higher risk of AEs. On the other hand, carbapenems–aminoglycoside combination therapy does not provide an advantage over carbapenems alone. Furthermore, the results were consistent when differences in therapy drug type and potential cofounders of the identified studies were considered. Meropenem and imipenem/cilastatin monotherapy appears to be available treatment for FN compared with β-lactams. Imipenem/cilastatin was related to higher risk of AEs. Balancing the evidence for drug efficacy and side effects, meropenem monotherapy appears to be available treatment for FN. In addition, empiric antimicrobial treatment of patients with FN should be selected in light of the local bacterial epidemiology and patterns of resistance. Further research may focus on subgroups such as patients with *Pseudomonas aeruginosa* or other pathogenic bacteria infection and other more critically ill patient subgroups.

Author contributions

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

References

[1] Barton CD, Waugh LK, Nielsen MJ, et al. Febrile neutropenia in children treated for malignancy. J Infect 2015;71:27–35.
[2] Kuderer NM, Dale DC, Crawford J, et al. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106:2258–66.
[3] Wisplinghoff H, Seifert H, Wenzel RP, et al. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis 2003;36:1103–10.
[4] Yadegarynia D, Tarrand J, Raad I, et al. Current spectrum of bacterial infections in patients with cancer. Clin Infect Dis 2003;37:1144–5.
[5] Montassier E, Batard E, Gastinne T, et al. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. Eur J Clin Microbiol Infect Dis 2013;32:841–50.
[6] Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis 2011;52:427–31.
[7] Baden LR, Swaminathan S, Angarone M, et al. Prevention and treatment of cancer-related infections, Version 2.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2016;14:882–913.
[8] El-Gamal MI, Brahim I, Hisham N, et al. Recent updates of carbapenem antibiotics. Eur J Med Chem 2017;131:185–95.
[9] Gupta N, Limbago BM, Patel JB, et al. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis 2011;53:60–7.
[10] Nemeth J, Oesch G, Kuster SP. Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis. J Antimicrob Chemother 2015;70:382–95.
[11] Higgins JP, Green S. Cochrane Reviewers' Handbook 5.3.0. Version 5.3.0. The Cochrane Collaboration; 2014. Available at: www.cochrane-handbook.org. Accessed Febuary 10, 2019.
[12] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[13] Kengkla K, Kongpakwattana K, Saokaew S, et al. Comparative efficacy and safety of treatment options for MDR and XDR Acinetobacter baumannii infections: a systematic review and network meta-analysis. J Antimicrob Chemother 2018;73:22–32.
[14] Dechartres A, Altman DG, Trinquart L, et al. Association between analytic strategy and estimates of treatment outcomes in meta-analyses. JAMA 2014;312:623–30.
[15] Hughes WT, Pizzo PA, Wade JC, et al. Evaluation of new anti-infective drugs for the treatment of febrile episodes in neutropenic patients. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis 1992;15:S206–15.
[16] Paul M, Yahav D, Bivas A, et al. Anti-pseudomonal beta-lactams for the initial, empirical, treatment of febrile neutropenia: comparison of beta-lactams. Cochrane Database Syst Rev 2010;10:CD005197.
[17] Paul M, Yahav D, Fraser A, et al. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother 2006;57:176–89.
[18] Paul M, Dickstein Y, Schlesinger A, et al. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. Cochrane Database Syst Rev 2013;29:CD003038.
[19] Horita N, Shibata Y, Watanabe H, et al. Comparison of antipseudomonal β-lactams for febrile neutropenia empiric therapy: systematic review and network meta-analysis. Clin Microbiol Infect 2017;23:723–9.
[20] Logan LK, Weinstein RA. The epidemiology of Carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. J Infect Dis 2017;215:28–36.
[21] Hsu LY, Apisarnthanarak A, Khan E, et al. Carbapenem-resistant Acinetobacter baumannii and Enterobacteriaceae in south and southeast Asia. Clin Microbiol Rev 2017;30:1–22.
[22] Righi E, Peri AM, Harris PN, et al. Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: systematic review and meta-analysis. J Antimicrob Chemother 2017;72:668–77.