Systematic Review and Meta-Analysis

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Meta-analysis: combination of meropenem vs ceftazidime and amikacin for empirical treatment of cancer patients with febrile neutropenia

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Abstract

Background: Meropenem monotherapy vs ceftazidime plus amikacin have been approved for use against febrile neutropenia. To assess the effectiveness and safety of them for empirical treatment of cancer patients with febrile neutropenia, we conducted a meta-analysis of randomized controlled trial.

Methods: Randomized controlled trials on ceftazidime plus amikacin, or/and monotherapy with meropenem for the treatment of cancer patients with febrile neutropenia were identified by searching Cochrane Library, PubMed, Science Direct, Wiley Online, Science Citation Index, Google (scholar), National Center for Biotechnology Information, and China National Knowledge Infrastructure. Data on interventions, participants' characteristics and the outcomes of therapy, were extracted for statistical analysis. Seven trials fulfilled the inclusion criteria.

Result: The treatment with ceftazidime plus amikacin was more effective than meropenem (OR = 1.17; 95% CI 0.93–1.46; 1270 participants). However, the treatment effects of the 2 therapy methods were almost parallel in adults (OR = 1.15; 95% CI 0.91–1.46; 1130 participants older than 16). Drug-related adverse effects afflicted more patients treated with ceftazidime plus amikacin (OR = 0.78; 95% CI 0.52–1.15; 1445 participants). The common responses were nausea, diarrhea, rash, and increased in serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and bilirubin.

Conclusion: Ceftazidime plus amikacin should be the first choice for empirical treatment of cancer patients with febrile neutropenia, and meropenem may be chosen as a last defense against pathogenic bacteria.

Abbreviations: CI = confidence intervals, OR = odds ratio.

Keywords: amikacin, ceftazidime, febrile neutropenia, meropenem, meta-analysis

1. Introduction enhanced myelosuppression

Since last decades, the survival rate of patients with malignancy had considerably increased resulting from improving chemotherapy.[1,2] However, the majority of cancer patients undergoing chemotherapy show febrile neutropenia (FN) which is a common side effect of myelosuppressive chemotherapy diagnosed as the reduced complete blood cell count. FN will make patients vulnerable to bacteria, fungi and viruses commonly encountered.[3] Reports indicated that patients with profound neutropenia were in high risk (approximately 90%) of acquiring life-threatening infectious complications.[4,5] In clinical management, prompt antimicrobial therapy, especially broad-spectrum antibiotic therapy, is applied at the onset of fever before the nature and susceptibility of the pathogen being detected in such infection.

Considering advantages of decreased toxicity and cost compared to multidrug regimens in many researches,[6–8] monotherapy with a broad-spectrum cephalosporin, such as ceftazidime and cefepime, or a carbapenem, is reported as an effective treatment [9–11] and suggested being used successfully as monotherapy.[12,13] Dr. Rejin Kebudi and the co-workers discover the beta lactam drugs cefepime and ceftazidime are effective and safe for the empirical treatment of febrile episodes in neutropenic patients.[14] As an ultra-broad spectrum antibiotic of the carbapenem group, meropenem is highly active in vitro against most of the gram-positive and gram-negative bacteria and anaerobes responsible for infections in neutropenic patients.[15] Unlike imipenem, meropenem is detected able to be given without

Editor: YX Sun.

This study was funded by grants from Youth Fund Research Project of Science and Technology of Hebei Colleges and Universities [QN2018147] and Doctoral Fund of Hebei University of Engineering.

Our goal is to publish this systematic review in a peer-reviewed journal. Since there are no issues about participant privacy, the review will not require ethical approval.

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Wang Y, Du Z, Chen Y, Liu Y, Yang Z. Meta-analysis: combination of meropenem vs ceftazidime and amikacin for empirical treatment of cancer patients with febrile neutropenia. Medicine 2021;100:8(e24883).

Received: 23 September 2020 / Received in final form: 8 December 2020 / Accepted: 9 December 2020

http://dx.doi.org/10.1097/MD.0000000000024883

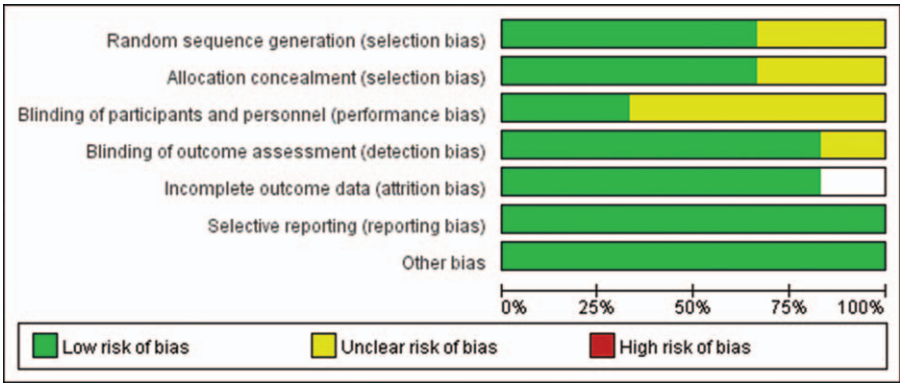

Figure 1. Risk of bias graph.

concomittant addition of Cilastatin. It is possibly the last line of defense against multi drug resistant gram-negative infections. It is noteworthy that meropenem should be used with caution and discretion especially, as there are not many drugs in the pipeline in the near future.[3] Therefore, combination therapy with a beta-lactam and an aminoglycoside has been traditionally recommended for febrile episodes in neutropenic patients at the same time.

Taken above, there are still confusions on the curative effect and safety of traditional combination therapy with ceftazidime plus amikacin vs monotherapy with meropenem. Collecting and analyzing the latest newly published articles since 1995, we performed a systematic review with meta-analysis of randomized control trails interfering the combination therapy with ceftazidime plus amikacin or/and monotherapy with meropenem in treatment of cancer patients with FN.

2. Materials and methods

2.1. Information sources and search strategy

The Cochrane Library, PubMed, ScienceDirect, Wiley Online, Science Citation Index (SCI), Google (scholar), National Center for Biotechnology Information, and China National Knowledge Infrastructure were searched for clinical trials on ceftazidime plus amikacin, or/and monotherapy with meropenem for the treatment of cancer patients with FN. This searching was performed with the following keywords: monotherapy, combination therapy, ceftazidime plus amikacin, meropenem, and FN in cancer. The published language was limited to English.

2.2. Eligibility criteria

The inclusion criteria were as followings:

1. randomized controlled trials (RCTs);
2. clinical trials on therapy of cancer patients with FN;
3. published from 1995 till now;
4. randomization procedure was performed;
5. interventions with meropenem and ceftazidime plus amikacin were conducted in trails;
6. scientific standard for curative effect;
7. reasonable exclusion criteria for participant selection.

Exclusion criteria were:

1. overlapping data;
2. not randomized studies;
3. only relevant to monotherapy or combination therapy;
4. review, abstracts, animal studies or letter;
5. in vitro activity only.

2.3. Data extraction

Titles and abstracts were scanned to filter out reviews, unavailable full articles and irrelevant ones by reviewers, independently. Then full texts of included studies were assessed for final quality eligibility basing on the consolidated standards of

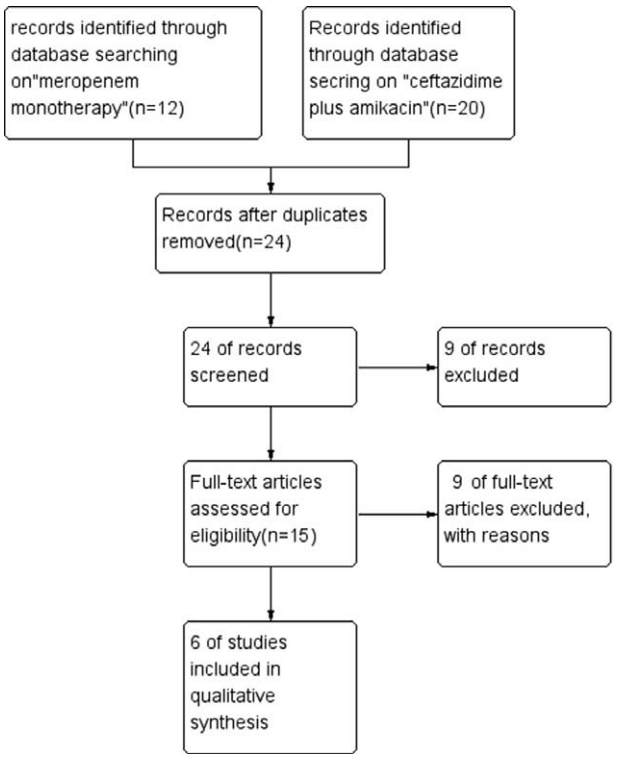

Figure 2. Flow diagram demonstrating studies processed for inclusion in the meta-analysis.

Table 1

Characteristics of all included studies in the meta-analysis.

Study IDs	Years	Interventions	Participants	M:F Ratio	Mean Ages (years)	Success Numbers	Failure	Adverse Effects
Hung-2003	2003	meropenem (40 mg/kg/does max 1g/dose q8h)	39	21/18	4.2 (0.7 ± 16.3)	28	10	not mentioned
		ceftazidime (50 mg/kg/does max 2 g/dose q8 hour) plus amikacin (5 mg/kg/does max 0.25 g/dose q8 hour)	37	24/13	3.6 (0.6 ± 12.4)	21	14	not mentioned
Agaoglu-2001	2001	meropenem alone (60 mg/kg/d i.v. in 3 doses)	30	1/8	6	22	8	in the meropenem arm, 3 patients had vomiting but no seizures
		ceftazidime (100 mg/kg/d i.v. in 3 doses) plus amikacin (15 mg/kg/d i.v. in 2 doses)	29		7	23	6	
		cefepime (100 mg/kg/d i.v. in 3 doses) plus netilmicin (5 mg/kg/d i.v. in 2–3 doses)	28		9	22	6	
Akova-1999	1999	meropenem (1 g tds)	40	25/15	36 (39 ± 17)	24	13	5.5% hypersensitivity; 11% transient increase in transaminases; 1% nausea and 1% diarrhoea
		ceftazidime (2 g tds) plus amikacin (1 g single daily)	43	25/18		22	18	17.5% transient increase in transaminases; 5% diarrhoea
Behre-1998	1998	Meropenem (1 g every 8 h by intravenous infusion for 20 ± 30 minutes)	34	22/12	46 (18 ± 76)	20	14	13% drug-related effects like nausea, diarrhoea and rash
		ceftazidime (2 g every 8 h by intravenous infusion) plus Amikacin (15 mg/kg per day in 2 or 3 equally divided doses)	37	24/13	50 (22 ± 70)	23	14	15% drug-related effects like diarrhoea and increase on SGOT, SGPT, Bilirubin
de la Camara-1997	1997	meropenem (1 g/8 hour)	46	22/24	42.2 (17 ± 71)	17	29	Erythema multiforme; Alkaline phosphatase increase; SGOT/SGPT increase
		ceftazidime (2 g/8 hour) plus amikacin (15 mg/kg/day)	47	27/20	41.6 (16 ± 66)	17	30	Renal function alteration; Rash; Deafness
Cometta-1996	1996	meropenem (1 g every 8 hour [q8 hour] for adults and children weighing more than 50 kg, 20 mg/kg q8 hour for children weighing less than 50 kg) infused over a period of 20 to 30 minutes	483	275/208	38 (1 ± 81)	270	190	151 of 516 (29%). However, only 19 patients (all adults) in the monotherapy arm experienced an adverse event considered related or probably related to the study drug.
		ceftazidime (2 g q8 hour for adults, 35 mg/kg q8 hour for children) plus amikacin (20 mg/kg/day given in a single daily dose)	475	266/209	39 (1 ± 77)	245	206	148 of 511 (29%). However, only 31 (30 adults and 1 child) in the combination arm experienced an adverse event considered related or probably related to the study drug.

SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamic pyruvic transaminase.

reporting trails.[16] The methodological quality of the trials was assessed with the Cochrane Collaboration Risk of Bias Tool in RevMan 5.3 for bias risk analysis.

Data from the included trials was extracted independently for quantitative analysis, and any disagreement was resolved by discussion subsequently. The primary information of study ID, published year, drug regimen and reverse effects were collected. The quantitative data included the patient characteristics, such as average age, sample size, sex ratio, value of successful case and failure case at the end of the study therapy.

2.4. Statistical analysis

Statistical analysis was performed using RevMan version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). Heterogeneity was explored using a Chi-Squared test, and the quantity of heterogeneity was measured using the I^2 statistic with Review Manager. $P \leq .10$ or $I^2 \geq 50\%$ suggests that there is heterogeneity and random-effect model should be chosen.[17] In experimental group, the first outcome was comparison on the success rate of meropenem vs control (ceftazidime plus amikacin) for empirical treatment of cancer patients with FN; the second outcome was the comparison of the failure rate; the third outcome was on the mentioned drug-related adverse effects. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for all outcomes were calculated with the Mantel-Haenszel fixed-effects.[18,19] For all analyses, results from the fixed-effect models are presented only when there was no heterogeneity between studies; otherwise, results from the random-effect models are presented. The reported results of outcomes of the analyzed studies were weighted by the inverse of their variance with the fixed-effect models.

3. Results

3.1. Characteristics of eligible studies

Relevant publications were retrieved from databases (PubMed, Google scholar, and SCI). As the outcome of assessment, Figure 1 showed the risk of bias for all the 6 included studies. A total of 15 relevant publications were adopted through reading records. After full-text scanning, 9 publications were excluded with reasons: 2 studies[20,21] were clinical trials single about combination therapy in FN patients with cancer; 3 publications[22–24] studied on monotherapy with meropenem only; while 2 publications[12,25] studied on the comparison of meropenem vs ceftazidime as empirical monotherapy; 1 study[26] was on cefepime vs meropenem; one of the full-text articles[27] were not available. (Fig. 2).

Eventually, 6 papers[28–33] were available for data extraction and assessment (Table 1). Inventions performed in 6 RCTs were all divided into 2 groups: meropenem group and ceftazidime plus amikacin group. Drug regimen of these 3 antibiotics varied according to verified empirical therapy so that the differences on doses between groups were negligible.

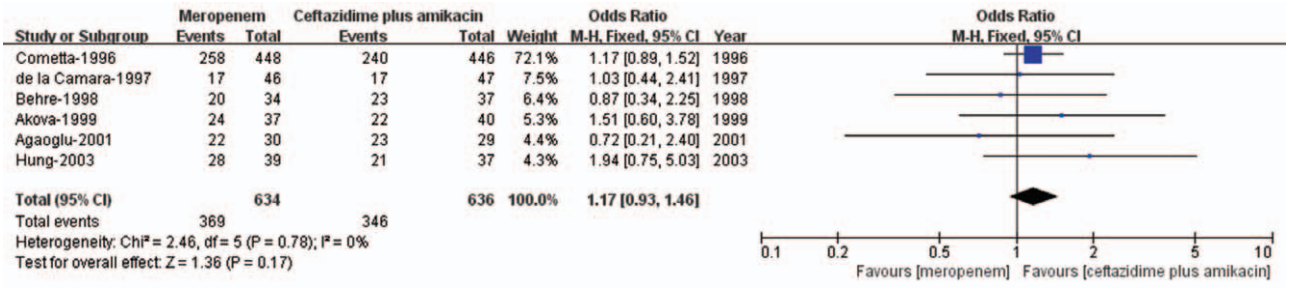

Figure 3. Comparison on the success rate of meropenem vs combined therapy with ceftazidime plus amikacin. The size of each square denotes the proportion of information given by each trial. Vertical line, "no difference" point in emergence of success cases treated by meropenem and ceftazidime plus amikacin; horizontal lines, 95% CIs = squares, ORs = diamond, pooled OR for all studies.

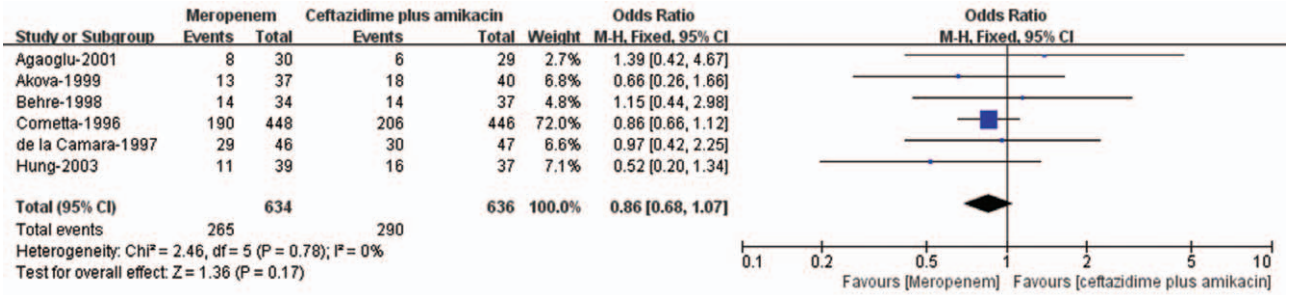

Figure 4. Failure rate of meropenem vs ceftazidime plus amikacin. The size of each square denotes the proportion of information given by each trial. Vertical line, "no difference" point in emergence of failure cases treated by meropenem and ceftazidime plus amikacin; horizontal lines, 95% CIs = squares, ORs = diamond, pooled OR for all studies.

3.2. Quantitative synthesis

In this analysis, participants treated by meropenem were considered as experimental cases, while the ones treated by ceftazidime plus amikacin were as control. In order to estimate the pharmaceutical effects of meropenem vs ceftazidime plus amikacin for empirical treatment of cancer patients with FN, only the cured or improved cases but not the undetectable or unchanged ones were considered as "events" in analysis.

No heterogeneity between studies had been identified in these outcomes ($Chi^2 = 2.46$, $df = 5$ ($P = .78$); $I^2 = 0\%$). The outcome of the comparison on the success rate indicated that the treatment effect of ceftazidime plus amikacin was better than meropenem monotherapy (OR = 1.17; 95% CI 0.93–1.46; 1270 participants) (Fig. 3). Meanwhile, failure rate of meropenem was higher than ceftazidime plus amikacin (OR = 0.86; 95% CI 0.68–1.07; 1270 participants) (Fig. 4). Analyzing the adverse effects, more patients suffered drug-related adverse effects when treated with ceftazidime plus amikacin (OR = 0.78; 95% CI 0.52–1.15; 1445 participants) (Fig. 5). (Table 2) Common responses were nausea, diarrhoea, rash, and increased in serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and bilirubin. For further understand the effect of drug to children and adults, data were sub-grouped on age (Table 3). Data of Cometta-1996[31] was not included in the adult group for existence of children without final treated data. In the sub-

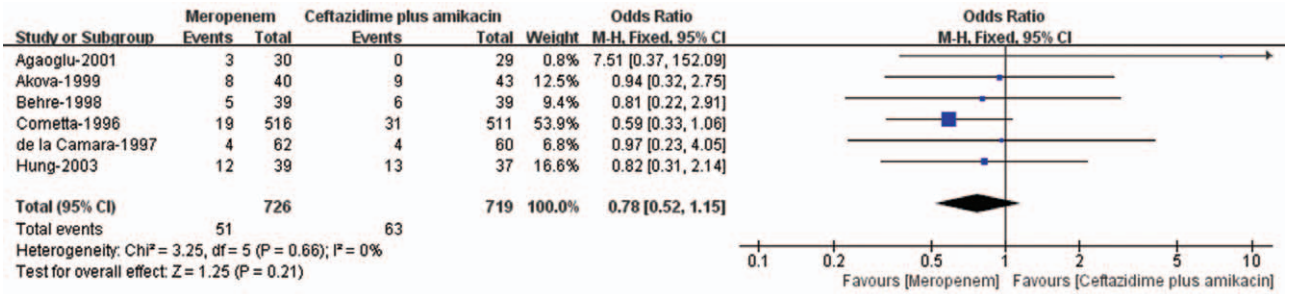

Figure 5. Outcomes of drug-related adverse effects from the 2 treatments. The size of each square denotes the proportion of information given by each trial. Vertical line, "no difference" point in emergence of adverse effects treated by meropenem and ceftazidime plus amikacin; horizontal lines, 95% CIs = squares, ORs = diamond, pooled OR for all studies.

Table 2

Outcomes without subgroup of analysis on treatment effects.

Outcome without Subgroup	Studies	Participants	Statistical Method	Effect Estimate
success case	6	1270	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.93, 1.46]
failure case	6	1270	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.68, 1.07]
adverse effect	6	1445	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.52, 1.15]

Table 3

Outcomes with subgroup of analysis on treatment effects.

Outcome and Subgroup	Studies	Participants	Statistical Method	Effect Estimate
success case	6	1270	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.93, 1.46]
adult	4	1135	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.91, 1.46]
children	2	135	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.63, 2.76]
failure case	6	1270	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.68, 1.07]
adult	4	1135	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.42, 2.25]
children	2	135	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.36, 1.58]

grouped outcome of the success cases, however, the treatment effects of the 2 therapy methods were almost parallel in adults (OR = 1.15; 95% CI 0.91–1.46; 1130 participants older than 16) (Fig. 6). No differences were identified in subgroup analysis of failure cases (Fig. 7). Articles mentioned adverse effects were all trails on adults.

3.3. Tests for publication bias and sensitivity analyses

Taken that the number of studies (N = 6) were too small to test for small study effects, publication bias was analysis only in funnel plot with Review Manager as showed in Figure 8.

4. Discussion

Patients with malignancy were in high risk of suffering chemotherapy-induced neutropenia, a significant dose-limiting toxicity in cancer treatment, leading to infection-related morbidity and mortality.[34] During neutropenic period, physicians must be keenly aware of the infection risks, diagnostic methods, and antimicrobial therapies required for febrile patients. Accordingly, researchers were very interested in the treatment of fever, neutropenia, and prophylaxis, treatment of infection.[35]

Prompt empirical antibiotic therapy using new broad-spectrum antibiotics such as carbapenems is becoming common even in patients with high-risk neutropenia of fever, replacing the traditional combination therapy.[29,30,36–38] As the newest member of this group of antibiotics, meropenem was also found as safe and effective as the combination of antibiotics (i.e., aminoglycoside plus beta-lactam such as ceftazidime) in large comparative trials. Considering this controversy, we preformed this review to estimate which treatment is more effective.

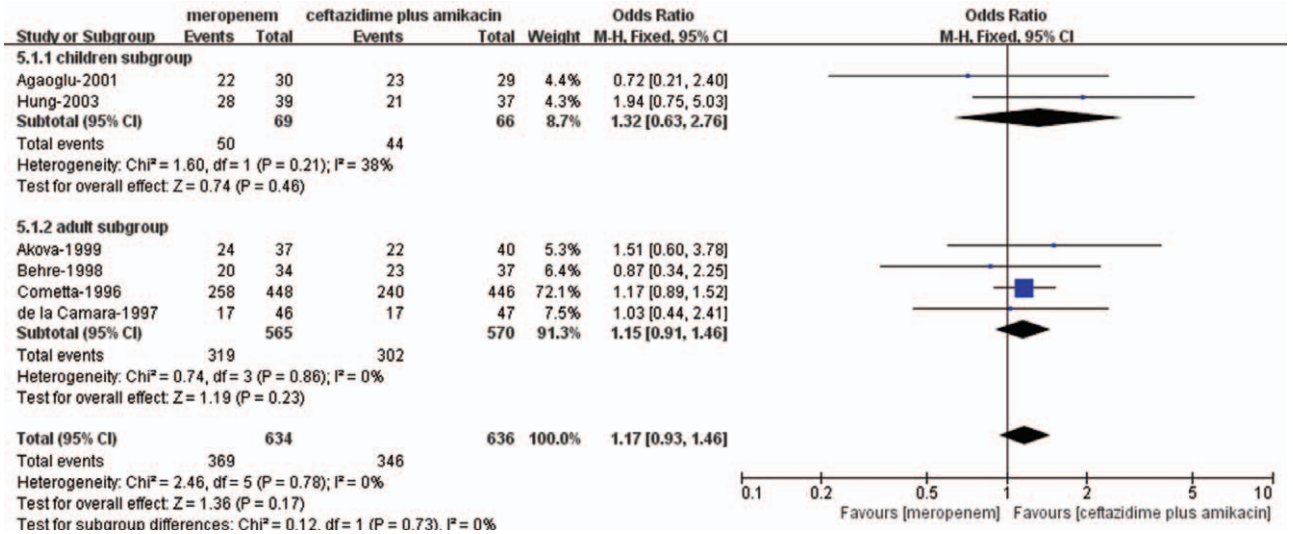

Figure 6. Sub-grouped outcome of the success cases. The size of each square denotes the proportion of information given by each trial. Vertical line, "no difference" point in emergence of success cases treated by meropenem and ceftazidime plus amikacin; horizontal lines, 95% CIs = squares, ORs = diamond, pooled OR for all studies. Grouped by age, adult, and children.

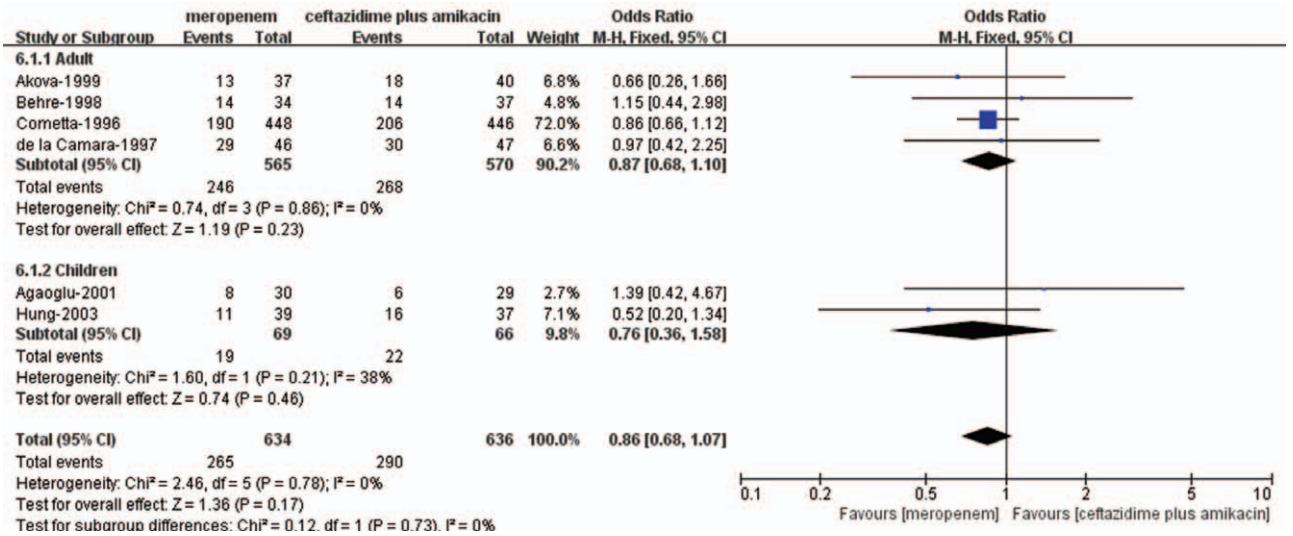

Figure 7. Subgroup analysis of failure cases. The size of each square denotes the proportion of information given by each trial. Vertical line, "no difference" point in emergence of failure cases treated by meropenem and ceftazidime plus amikacin; horizontal lines, 95% CIs = squares, ORs = diamond, pooled OR for all studies. Grouped by age, adult, and children.

Since 1995, there were not many articles of clinical trials on monotherapy with meropenem vs combination therapy of ceftazidime plus amikacin for empirical treatment of cancer patients with FN. With small sample data, we applied fixed-effects meta-analysis model (Mantel-Haenszel method) for analysis. Considering treatment effect and failure rate, meropenem was not ideal comparing with ceftazidime plus amikacin, especially in children. In contrast, previous studies had reported meropenem was effective and well-tolerated when used for the treatment of neutropenic cancer children against most beta-lactamases produced by gram-negative bacteria.[23] As for there was no review on the effect of meropenem versus ceftazidime plus amikacin in this disease, this result was still valuable reference for clinical management. In addition, monotherapy indeed own significant advantages in preventing treatment failures and reducing adverse effects. Researchers indicated that the high activity of meropenem could be explained by ease of entry into bacteria, combining to essential penicillin binding proteins, including those associated with cytolysis. Although meropenem had a broad antibacterial spectrum due to stability to all serine-based β-lactamases, it was slightly less active against staphylococci and enterococci.[24] In this respect, a combined therapy was superior. In subgroup analysis, superiority was not that significant in adults. An explanation was that a slight change in dosage might cast a dramatic effect on the pharmacological action and pharmacokinetics. Moreover, it was observed that duration of FN was significantly longer in patients with an absolute neutrophil count (ANC) of less than 100/mm^3 and even in those with an ANC of less than 200/mm^3, and in children who were not in remission for the malign disease.[22]

Drug-related effects like diarrhoea, increased in SGOT, SGPT and bilirubin, nausea, vomiting, abdominal pain, headache, rash and vertigo were side effects of therapy with both methods, but they were well tolerated. In review, the observed toxicity in combined therapy was higher than that in meropenem, but did not lead to withdrawal from therapy.

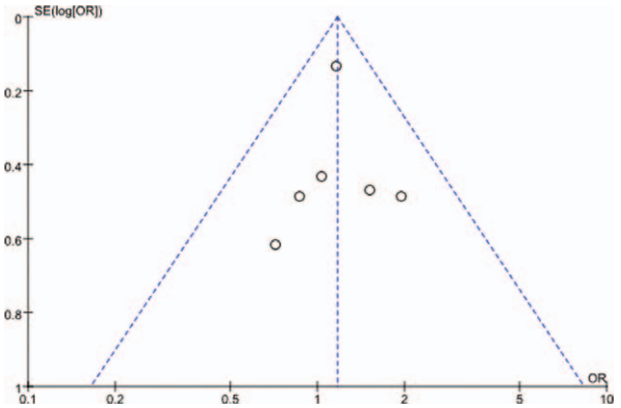

Figure 8. Publication bias was analysis only in funnel plot with Review Manager.

5. Conclusion

Efficacy of monotherapy with meropenem was less than that of combined therapy with ceftazidime plus amikacin for empirical treatment of cancer patients with FN. However, the usage of meropenem was safer with less adverse effect. As a clinical reference, we suggest combination therapy as first priority, and meropenem could be chosen as the last defense against pathogenic bacteria. Meanwhile, considering the small sample amount of the included trials, more studies and analysis were still needed.

Author contributions

Conceptualization: Yugang Liu, Zhitang Yang.
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Funding acquisition: Yugang Liu, Zhitang Yang.
Formal analysis: Ying Wang, Zhichao Du, Yongdong Chen, Yugang Liu.

Investigation: Ying Wang, Yongdong Chen, Yugang Liu.
Methodology: Ying Wang, Zhichao Du, Yongdong Chen.
Project administration: Ying Wang, Yugang Liu, Zhitang Yang.
Resources: Zhichao Du.
Software: Zhichao Du, Yongdong Chen.
Supervision: Yugang Liu, Zhitang Yang.
Writing – original draft: Ying Wang, Yugang Liu, Zhitang Yang.
Writing – review & editing: Yugang Liu, Zhitang Yang.

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