

Comparative efficacy and safety of β -lactam/ β -lactamase inhibitors versus cabapenems for febrile neutropenia empiric therapy: A systematic review and meta analysis

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Abstract

Background

The efficacy and safety of β -lactam/ β -lactamase inhibitors (BL/BLIs) versus carbapenems for febrile neutropenia empiric therapy are controversial.

Methods

PubMed, Embase, Cochrane library databases, Web of Science and Google scholar were searched up to 1 April 2020. Studies were included if they compared BL/BLIs versus carbapenem for febrile neutropenia patients undergoing chemotherapy for either solid tumours or haematological malignancies among adults and children. We pooled the treatment success rate, mortality and adverse events.

Results

Nine RCTs were included. There was no differences between carbapenems and BL/BLIs were observed in terms of treatment success without modification (RR 1.04, 95% CI 0.93–1.15), no differences were observed in the subgroups of BL/BLIs, adults and children. No significant differences were found in all-cause mortality (RR 1.15, 95% CI 0.64–2.06). Our study shows that gastrointestinal events are the most common adverse effects, nausea/vomiting were significantly more common with carbapenems (RR 2.83, 95% CI 1.35–5.92, $P=0.006$), however, diarrhea were more common with BL/BLIs (RR 0.47, 95% CI 0.27–0.80, $P=0.006$).

Conclusions

The efficacy and safety of BL/BLIs with carbapenems were comparable in empiric treatment of febrile neutropenia.

Introduction

Despite improvements in cancer management, febrile neutropenia (FN) remains a serious complication of cancer chemotherapy, with significant morbidity, mortality and healthcare resource use[1]. Broad spectrum β -lactams such as imipenem/cilastatin, meropenem, piperacillin/tazobactam and amoxicillin/clavulanate are recommended for patients with febrile neutropenia by guidelines[2, 3]. In addition, other β -lactam/ β -lactamase inhibitors (BL/BLIs) such as cefoperazone/sulbactam and ceftolozane/tazobactam have also been investigated in febrile neutropenia patients[4, 5]. However, despite many trials had been conducted, no clear conclusions to be drawn which empirical therapeutic regimen for febrile neutropenia empiric therapy is better than others[3]. In recent years, the increasing proportion of multidrug-resistant bacteria in hematology patients has become a global concern[6]. Carbapenem de-escalation strategy for hematology patients would be useful for controlling antimicrobial resistance[7, 8]. Gudiol *et al.* compared the efficacy of BL/BLIs to carbapenems in two cohorts of hematological neutropenic patients with extended-spectrum- β -lactamase (ESBL) bloodstream infection (BSI) and found similar results in 30-day case fatality rates and other secondary outcomes, the authors concluded that BL/BLIs might be carbapenem-sparing alternatives for the treatment of BSI by ESBL-producing bacteria[9].

Although previous systematic reviews compared the effectiveness of piperacillin/tazobactam with carbapenem, conflicting results related to mortality were found[10, 11]. No meta-analysis has compared BL/BLIs with carbapenems for treating febrile neutropenia. Therefore, we conducted a systematic review and meta analysis of randomized trials (RCTs) that compared BL/BLIs versus carbapenems for febrile neutropenia empiric therapy.

Methods

Search strategy

We performed a systematic review in accordance with the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA)[12]. A comprehensive search of the PubMed, Embase, Cochrane Library, Web of Science and Google scholar and ClinicalTrials. Additionally, a manual search of the retrieved articles, related review articles, and meta-analyses was conducted to identify other relevant articles. The search covered the time from each database's inception to 1 April 2020. We used the following key terms and their combination without language restrictions: "clavulanic", "sulbactam", "tazobactam", "avibactam", "beta-Lactamase Inhibitors", "imipenem", "meropenem", "biapenem", "ertapenem", "doripenem", "panipenem", "carbapenems", "neutropenia", "granulocytopeni*", "granulocytopaeni*", "neutropeni*", "neutropaeni*", "leukocytopeni*". The details of the search strategy can be found in the Supplementary S1.

Inclusion and exclusion criteria

The definitions of febrile neutropenia can vary but should not deviate too much from guidelines: the cutoff neutrophil counts per liter were either 500 or 1000, and the definitions of fever were a single oral temperature of $>38.3^{\circ}\text{C}$ (101°F) or a temperature of $>38.0^{\circ}\text{C}$ (100.4°F) sustained for >1 hour[2, 3, 13]. We included RCTs comparing any BL/BLI versus any carbapenem for febrile neutropenia patients undergoing chemotherapy for either solid tumours or haematological malignancies among adults and children. Febrile neutropenic patients were randomly assigned to receive either BLBLs or carbapenem

group antibiotics, adding the same antibiotic/treatment for both arms was accepted. The primary outcome was treatment success without modification of the antibiotic regimen, the secondary outcomes were all-cause mortality, infection related mortality and adverse events (AEs).

Study selection and data extraction

After eliminating duplicates by EndNote X9 software and manual check. Two reviewers (HY MENG and JY ZHANG) independently reviewed the titles and abstracts of records retrieved from the search and selected all potentially relevant studies according to the pre-defined inclusion and exclusion criteria. A pilot search was conducted before the full screening of the literature to ensure that each reviewers understood the screening criteria and process. Disagreements about selection of studies were resolved by consulting a third party (AL ZHANG). The process of study selection was documented using a PRISMA flow diagram[14].

Two reviewers (HY MENG and JY ZHANG) independently extracted the following data from included trials using a standardized extraction sheet: 1) basic information (year of publication, first author and affiliation, journal, funding, conflict of interest; 2) study details (study design, sample size, research population characteristics, interventions, outcomes). A pre-test was conducted before formal extraction to ensure that each researcher agreed with the extraction criteria and process. Disagreements were solved through discussion with a third party (AL ZHANG).

Risk of bias assessment

Two reviewers (AL ZHANG and J YANG) assessed the quality of the included studies independently. We used the Cochrane bias risk assessment tool (Risk of bias) to assess the randomized controlled trials[15], examining the generation of the allocation sequence, allocation concealment, blinding, assessment of incomplete outcome data, selective outcome reporting, other basis (e.g. early conclusion of the trial and extreme imbalance at baseline).

Data synthesis

For the dichotomous variables, the risk ratios (RRs) were calculated and reported with the 95% CIs. The heterogeneity of the studies was measured using the I^2 statistics and the Q test (heterogeneity χ^2). A Q test result of $P < 0.1$ or $I^2 > 50\%$ indicates heterogeneity, the random-effects model was applied. If heterogeneity was absent in a study, a fixed-effects model was used. The meta analysis was conducted using RevMan 5.3.

We conducted subgroup analyses for the primary outcome according to the following patient subgroups: 1) adults versus children; 2) types of BL/BLIs. We found an insufficient number of studies to allow review authors to undertake sensitivity analysis to determine the effect of including/excluding studies with high risk of bias (e.g. as a result of inadequate concealment of allocation).

We assessed potential risk of publication bias through visual analysis funnel plot symmetry and egger's test by STATA 13.

Results

We identified 2173 articles in the initial literature search (Figure S1). After removing duplicates, we screened the titles and abstracts of 1864 records. 42 articles were retrieved for full-text reviewing. Finally, nine RCTs involved 1925 episodes of patients that compared BL/BLIs with carbapenems fulfilled the inclusion criteria for this study[16–24]. Three[17, 20, 23] of the 9 studies were conducted in Turkey, two[16, 24] were conducted in USA; and one study was conducted in Spain[18], Germany[21], China[19] and Japan[22]. These studies were conducted between 1996 and 2017. Seven studies[16, 17, 20–24] focused on haematological malignancy and solid malignancy; one study[19] focused on haematological malignancy and one study[18] was not specified. Five studies[16, 19–21, 24] included only adults, two[17, 23] included only children, one study[22] included mainly children, and the other one[18] did not provide the patient age. Among the 9 trials, piperacillin/tazobactam was evaluated in 6 trials[18–23] and cefoperazone/sulbactam in evaluated in 3 trials[16, 17, 24]. Amikacin was added to the treatment groups in one study[20] and vancomycin was used in another study[16] (Table 1).

Table 1
Characteristics of included studies.

Study	Country	Age(median, range)		Episodes of patients	Dose regimen		Outcomes	Timing of evaluation for treatment success without modification	Mortality observation duration
		Carbapenems	BL/BLIs		Carbapenems	BL/BLIs			
Bodey <i>et al.</i> 1996[16]	USA	50(18–79)	52(17–84)	369	IPM(500 mg/m ² × 4) + VAN(1g × 2)	CFS(3g × 3) + VAN(1g × 2)	☐,☐	End of treatment	NA
Winston <i>et al.</i> 1998[24]	USA	39(16–81)	47(16–76)	203	IPM(0.5g × 4)	CFS(6g × 2)	☐,☐,☐	End of treatment	NA
Figuera <i>et al.</i> 2001[18]	Spain	NA	NA	137	IPM(0.5g × 4)	TZP(4.5g × 4)	☐,☐,☐,☐	72 h after treatment	NA
Reich <i>et al.</i> 2005[21]	Germany	44(18–70)	44(20–63)	232	MEM(1g × 3)	TZP(4.5g × 3)	☐,☐,☐	72 h after treatment	7 d after treatment
Oztoprak <i>et al.</i> 2010[20]	Turkey	52.79(17–83)		120	MEM(1g × 3) + AMK(1g × 1) IPM(0.5g × 4) + AMK(1g × 1)	TZP(4.5g × 4) + AMK(1g × 1)	☐,☐,☐	End of treatment	End of treatment
Vural <i>et al.</i> 2010[23]	Turkey	4(2–13)	5(2–14)	99	IPM(15 mg/kg × 4)	TZP(90 mg/kg × 4)	☐,☐,☐	End of treatment	During neutropenia
Demir <i>et al.</i> 2011[17]	Turkey	7.5(0.58–17.4)	5.7(0.5–17.16)	208	IPM(20 mg/kg × 3) MEM(20 mg/kg × 3)	CFS(60 mg/kg × 3)	☐,☐,☐	72 h after treatment	During treatment
Jing <i>et al.</i> 2016[19]	China	40(25–50)	41(25–48)	123	IPM(0.5g × 4)	TZP(4.5g × 4)	☐,☐,☐	End of treatment	During treatment
Sano <i>et al.</i> 2017[22]	Japan	10(0–25)	9(0–25)	434	MEM(40 mg/kg × 3)	TZP(112.5 mg/kg × 3)	☐,☐,☐,☐	120 h after treatment	NA
IPM: imipenem/cilastatin, VAN: vancomycin, MEM: meropenem, CFS: cefoperazone/sulbactam, TZP: piperacillin/tazobactam, AMK: amikacin.									
h: hour, d: day, NA: not available.									
☐: treatment success without modification, ☐: all-cause mortality, ☐: infection related mortality, ☐: adverse event									

More than half of the studies were assigned unclear risk of bias related to random sequencing, allocation concealment and blinding. One trial was judged as high risk by lack of blinding. High risk of bias in incomplete outcome data were assigned because of the lack of data related to mortality and major outcomes. Three trials funded by pharmaceutical company were assigned high risk in other bias. (Fig. 1).

Treatment success without modification

Treatment success without modification was evaluated in 9 studies including 1925 episodes, with no difference between carbapenems and BL/BLIs in empiric treatment of febrile neutropenia (RR 1.04, 95% CI 0.93–1.15) (Fig. 2).

In a subgroup analysis including studies only for adults, carbapenems had a similar treatment success rate with BL/BLIs (RR 1.04, 95% CI 0.90–1.20). In a subgroup analysis including studies only for children, no significant difference between carbapenems and BL/BLIs in treatment success rate (RR 0.99, 95% CI 0.86–1.14) (Figure S2).

In a subgroup analysis by BL/BLIs, the pooled analysis of 6 studies showed carbapenems had a treatment success rate similar with piperacillin/tazobactam (RR 1.07, 95% CI 0.92–1.23), and cefoperazone/sulbactam (RR 0.97, 95% CI 0.90–1.04) (Figure S3).

In the sensitivity analysis after studies were randomly excluded, similar RRs were observed ($I^2 = 43\%$). After excluding a study that only focused on haematological malignancy, heterogeneity (I^2) between studies was less than 50%.

The funnel plot for treatment success without modification was approximately symmetrical (Fig. 3). Egger's test was conducted to assess publication bias and no evidence of asymmetry was observed in treatment success without modification ($P = 0.222$).

All-cause mortality

All-cause mortality was reported in 7 studies, including 1457 episodes. No significant difference between carbapenems and BL/BLIs in mortality was observed (RR 1.15, 95% CI 0.64–2.06) (Fig. 4).

Infection-related mortality

Only two studies reported on the infection related mortality, including 637 episodes. A difference in favour of carbapenems was observed, but this difference was not statistically significant (RR 0.45, 95% CI 0.07–3.05) (Fig. 5).

Adverse events

Risk of nausea/vomiting was higher in the carbapenems arm compared with BL/BLIs (RR 2.83, 95% CI 1.35–5.92, $P=0.006$). Inversely, BL/BLIs were associated with a significant increase in the risk of diarrhea relative to carbapenems (RR 0.47, 95% CI 0.27–0.80, $P=0.006$). In addition, no significant difference was observed for rash (RR 0.87, 95% CI 0.39–1.92), hepatotoxicity (RR 1.16, 95% CI 0.31–4.40), and seizure (RR 4.05, 95% CI 0.68–24.31) (Fig. 6).

Discussion

To the best of our knowledge, this is the first study to compare BL/BLIs and carbapenems in empiric treatment of febrile neutropenia. No significant difference was found between BL/BLIs and carbapenems in treatment success without modification. Similar results were observed in pooled analyses both adults and children in subgroup analysis. Treatment success rate of our findings are consistent with the network meta-analysis published by Horita *et al.* in 2017[11] which combined direct and indirect estimates. Another meta-analysis for cefoperazone/sulbactam in empiric therapy for febrile neutropenia by Lan *et al.* reported that cefoperazone/sulbactam had a treatment success rate similar to piperacillin/tazobactam and carbapenems[25]. Our study also revealed both piperacillin/tazobactam and cefoperazone/sulbactam had a similar success rate compared with carbapenems in subgroup analysis.

In terms of mortality, We found no differences between BL/BLIs and carbapenems in all cause mortality or infection related mortality. A meta-analysis for initial empirical treatment of febrile neutropenia by Paul *et al* reported that mortality was significantly lower with piperacillin/tazobactam compared with carbapenems (RR 0.46, 95% CI 0.22–0.95)[10]. Lan *et al.* reported that cefoperazone/sulbactam was not significantly different with other comparators in mortality through pooled analysis (OR 0.96, 95% CI 0.58–1.58) [25]. Recently a single-center retrospective cohort study conducted by Benanti *et al.* showed empiric treatment with cefepime or piperacillin-tazobactam was not associated with increased 14-day mortality in neutropenic patients with hematologic malignancy and ESBL-producing *E. coli* bacteremia relative to that with empiric treatment with a carbapenem[26]. These findings favor the use of BL/BLIs in empiric treatment of febrile neutropenia.

Adverse events were slightly more common with carbapenems, but there was no statistical difference. Our study shows that gastrointestinal events are the most common adverse effects, nausea/vomiting were significantly more common with carbapenems. According to a previous systematic review included 21 trials by Shiber *et al.*, diarrhea was significantly more common with BL/BLIs (RR 1.46, 95% CI 1.25–1.70)[27], which was consistent with our result from pooled analysis. In addition, higher rates of *Clostridium difficile* associated diarrhea were reported with carbapenems compared with BL/BLIs by Shiber *et al.*. This finding could not be supported by our review owing to limited reporting on *Clostridium difficile* in the included trials.

There are several limitations for this review. First, definitions of febrile neutropenia and timing of evaluation for treatment success were inconsistent across studies. Second, allocation concealment and blinding were unclear in most trials. Third, the number of people included in our study were low, a large scale RCT comparing a BL/BLI with a carbapenem should be conducted to confirm our findings.

Conclusions

We conducted a systematic review and meta-analysis involved 9 RCTs to compare BL/BLIs with carbapenems for febrile neutropenia empiric therapy. Our study shows no advantage of carbapenems over BL/BLIs in terms of treatment success rate and mortality, with more adverse events likely to occur supporting the use of BL/BLIs for empiric febrile neutropenia treatment. Well-designed RCTs are needed in order to support the beneficial effects of BL/BLIs for febrile neutropenia empiric therapy in the future.

Declarations

Funding:

This study was carried out as part of our routine work.

Availability of data and materials:

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Conflict of interests:

None of the authors have any conflicts of interest.

Authors' contributions:

Haiyang MENG conceived and designed the study, drafted of the manuscript. Jingyi ZHANG contributed in comprehensive research. Ailing ZHANG Jingli LU designed the figures. Yanfang Ma and Qi ZHOU contributed in manuscript editing. Jian KANG and Xiaojian ZHANG revised the manuscript and approved the final version to be published. The author(s) read and approved the final manuscript.

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Figures

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bodey 1996	+	+	●	+	+	●	●
Demir 2011	?	?	?	?	+	+	?
Figuera 2001	?	?	?	?	?	●	?
Jing 2016	?	?	?	?	+	+	?
Oztoprak 2010	+	?	?	?	+	+	?
Reich 2005	+	?	?	?	+	+	●
Sano 2017	?	?	?	?	+	+	?
Vural 2010	?	?	?	?	+	+	?
Winston 1998	?	?	?	?	+	+	●

Figure 1

Risk of bias summary for each included study

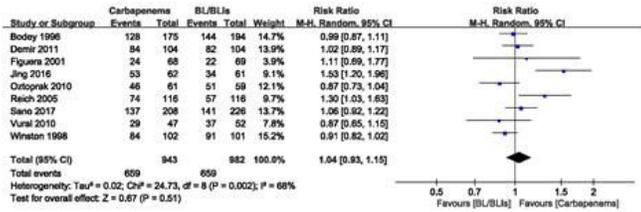


Figure 2

Forest plot for treatment success without modification

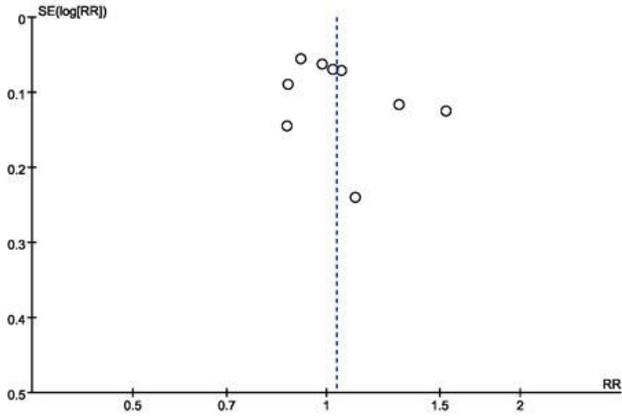


Figure 3

Funnel plot for treatment success without modification

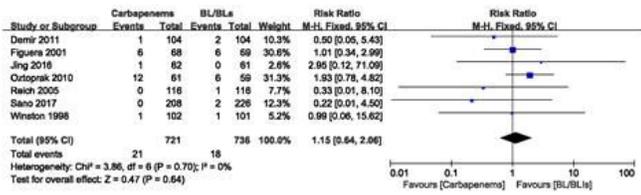


Figure 4

Forest plot for all-cause mortality



Figure 5

Forest plot for infection-related mortality

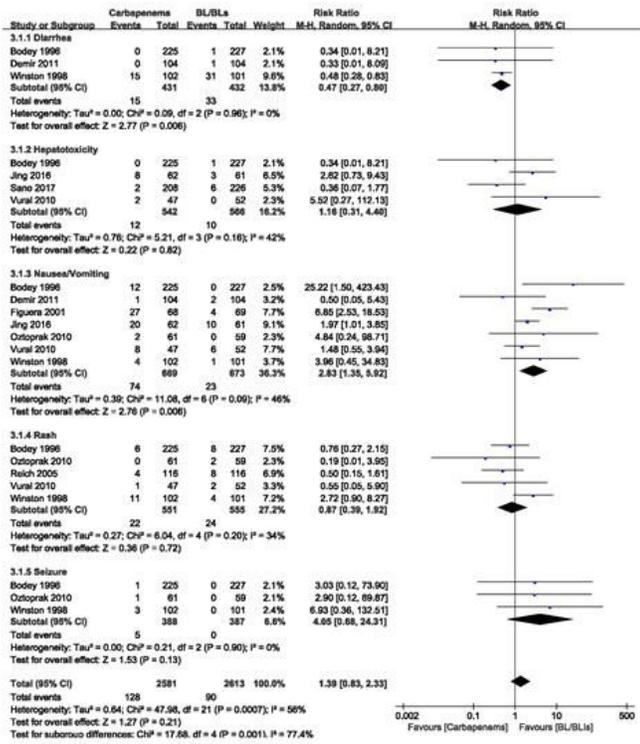


Figure 6

Forest plot for adverse events

Supplementary Files

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- [Supplementarydata.doc](#)