Carbapenems *versus* β-lactam and β-lactamase inhibitors for treatment of nosocomial pneumonia: A systematic review and meta-analysis

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A B S T R A C T

Background: Carbapenems and β-lactam and β-lactamase inhibitors (BLBLIs) have been used empirically in nosocomial pneumonia, but their efficacy and safety are controversial.
Objective: We carried out a systematic review with meta-analysis to evaluate the efficacy and safety of carbapenems versus BLBLIs against nosocomial pneumonia.
Methods: PubMed, Embase, Cochrane Central Register of Controlled Trials, CNKI, Wangfang, VIP and Sinomed were searched systematically through April 29, 2023 for clinical trials comparing carbapenems with BLBLIs for treatment of nosocomial pneumonia. Random-effects models were used to evaluate the impact of treatment on the risk ratio (RR) of all-cause mortality, clinical response, microbiologic response, resistance by *Pseudomonas aeruginosa*, adverse effects (AEs), and serious adverse effects. The quality of the evidence was assessed with the Cochrane risk of bias tool. The review was registerted in the INPLASY (INPLASY202340113).
Results: Seven randomized controlled trials containing 3306 patients met our inclusion criteria Our meta-analysis showed no significant difference in all-cause mortality (RR = 0.88, 95% confidence interval [CI] = 0.75–1.03, I^2 = 0%) or clinical cure (1.02, 0.96–1.09, 30%) or clinical failure (1.19, 0.97–1.47, 0%) or microbiologic clinical cure (0.98, 0.89–1.06, 40%) or *Pseudomonas aeruginosa* resistance (RR 2.43, CI 0.86–6.81, 49%, P = 0.09) or adverse events (0.98, 0.93–1.02, 0%) between carbapenems groups *versus* BLBLIs groups, but a significant difference was found for severe adverse events (RR 0.83, CI 0.73–0.94, 0%).
Conclusion: Differences in the prevalence of mortality, clinical cure, or clinical failure were not observed between carbapenems groups *versus* BLBLIs groups in terms of nosocomial pneumonia. The use of carbapenems was linked to a tendency towards the emergence of *P. aeruginosa* resistance, however, no statistically significant difference was observed.

1. Introduction

Hospital-acquired pneumonia (HAP) is one of the most common types of infection of pulmonary parenchyma and includes ventilator-associated pneumonia (VAP). A survey estimated 157,500 infections occur in the USA [1]. HAP (particularly VAP) has

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become a major public health issue due to its high morbidity and mortality rates. All-cause mortality (ACM) is associated with a VAP prevalence of 20%–50% [2]. A recent study estimated that the cost of caring for a patient with VAP was $40,144 [3].

The European Respiratory Society (ERS) Guidelines have recommended broad-spectrum empiric antibiotic therapy to cover infections by *Pseudomonas aeruginosa* and other Gram-negative bacteria for treatment of HAP/VAP patients [4].

Carbapenems have broad-spectrum antibacterial activity and can be employed against *P. aeruginosa* and other Gram-negative bacteria. Carbapenems have become a common option in nosocomial pneumonia caused by Gram-negative bacteria. However, several studies have demonstrated that use of carbapenems is resistance to their effects [5]. Administration of inappropriate initial antibiotic therapy in a patient with HAP is a high-risk factor causing multidrug-resistant (MDR) Gram-negative bacteria. Inadequate antibiotic therapy has been associated with significantly increased mortality [6]. Identifying the appropriate initial antibiotic therapy for HAP is very important.

We undertook a meta-analysis of the effects and safety of carbapenems *versus* BLBLIs in patients with HAP. We compared the differences in mortality, clinical response, microbiologic response, and side-effects between carbapenems *versus* BLBLIs.

2. Methods

2.1. Search strategy

The meta-analysis was conducted according to the PRISMA statement [7], as demonstrated by the PRISMA checklist provided in the Supplementary Material 1 and was registered on the International Platform of Registered systematic Review and Meta-analysis Protocols (INPLASY202340113). Two authors (Huai-Qin Cang and Xiang-Hua Quan) searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, CNKI, Wanfang, VIP and Sinomed independently from inception until November 03, 2021, and the updated search was completed on April 29, 2023 to investigate use of carbapenems against nosocomial pneumonia. The search terms we used were "carbapenem", meropenem*, imipenem*, "doripenem, "biapenem", ertapenem*, "panipenem", "razupenem", and "tomopenem". We also retrieved reference lists of articles. The outcomes of this retrieval strategy are shown in Supplementary Material 2. We included studies written in English or Chinese.

2.2. Inclusion criteria

(1) Participants: Patients had to be diagnosed with HAP (including VAP). Pneumonia had to be diagnosed based on clinical and radiographic criteria: purulent tracheal secretions with at least one respiratory sign or symptom of pneumonia, including new-onset fever or hypothermia, leukocytosis, or decline in oxygenation and including new or worsening infiltrates on chest radiographs within 48 h of hospital admission. HAP was defined as a patient with pneumonia who remained in hospital ≥48 h after hospital admission. VAP was defined as pneumonia with onset ≥48 h after endotracheal intubation and mechanical ventilation. (2) Interventions: The experimental group had to be treated with carbapenems. (3) Comparaors: The control group had to be treated with BLBLIs. (4) Outcomes: The primary outcomes were mortality and clinical response. Secondary outcomes were the microbiologic response, resistance by *Pseudomonas aeruginosa* and side-effects of antibiotic treatment. (5) Study design: a randomized control trial (RCT).

2.3. Exclusion criteria

(1) Abstracts, conference papers; (2) studies with incomplete data or using different control drugs; (3) articles not written in English or Chinese.

Two authors extracted data independently. Disagreement was resolved by discussion until consensus was reached, or by consulting a third author.

2.4. Data extraction

The following data were extracted by two reviewers independently: author names; year of publication; the country where the study was conducted; number of participants; sample size; age distribution; ratio of males: females; study design; intervention; drug dose; patient characteristics at baseline; comparator; outcome information. Disagreements between the two data extractors were resolved by consensus reached from all authors.

2.5. Risk of bias and GRADE assessments of evidence

Two reviewers assessed the quality of selected studies independently according to the Cochrane Collaboration's tool for RCTs [8]. Items were evaluated in three categories: "low" "unclear", and "high" risk of bias. The following characteristics were evaluated: random-sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel to the study protocol (performance bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias).

We evaluated the confidence in the evidence for each outcome by employing the GRADE approach, which considers study design, risk of bias, inconsistency, indirectness, imprecision [9–13]. The GRADE confidence levels are displayed in Table 3.

2.6. Statistical analysis

Review Manager 5.4 was used for this meta-analysis [14]. Treatment effects were calculated with the risk ratio (RR) and the corresponding 95% confidence interval for dichotomous outcomes. Cochran's Q statistic (significance level, P<0.01) and I^2 statistic were employed to assess heterogeneity. According to the *Cochrane Handbook*, I^2 can be considered "non-important" (<30%), "moderate" (30%–60%), and "substantial" (>60%) [8]. Heterogeneity can be categorized into three types: clinical heteogeneity, methodological heterogeneity and statistical heterogeneity. Although statistical heterogeneity was not present, there was still clinical heterogeneity, and therefore, the radom-effects model was employed to improve the reliability of the result. Results were assessed using forest plots. Sensitivity analysis was undertaken to ascertain the results of the meta-analysis by excluding each individual study. Subgroup analyses were conducted according to the type of carbapenems, the classification of microorganisms and categorization of AEs. In this systematic review, we limited our examination to less than 10 literature sources and as a result, were unable to assess pubication bias using funnel plot.
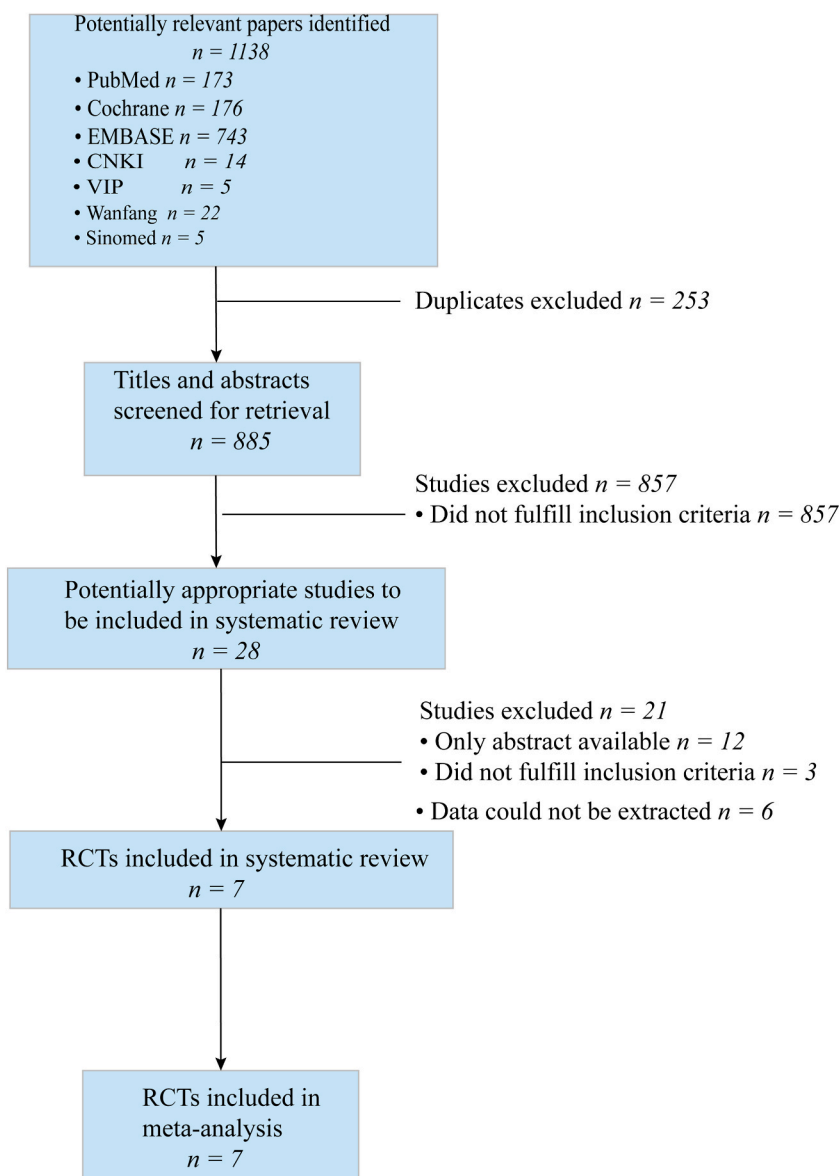

Fig. 1. Flow diagram of literature search and study selection.

Table 1
Characteristics of included studies.

Country	Number of participants	Design	Experimental group						Control group						Outcome
			Sample size	Age (year)	Female (%)	Intervention	dose	APACHE II	Sample size	Age (years)	Female (%)	APACHE II	Intervention	dose	
Switzerland	154	RCT, 2 arms	79	59.76 ± 16.9	34.20%	Imipenem–cilastatin	0.5 g q6h	14.9 ± 6.8	75	56.6 ± 17.6	22.70%	14.6 ± 6.8	Piperacillin-tazobactam	4.5 g q8h	clinical-failure、clinical-success、Death due to infection、Resistance、mortality、P.aeruginosa clinical cure
USA	437	RCT, 2 arms	215	52.7	36.00%	Imipenem–cilastatin	0.5 g q6h	13	222	53.2	22.00%	13.9	Piperacillin-tazobactam	4.5 g q6h	Clinical cure、*Pseudomonas aeruginosa* Eradication、*Klebsiella pneumoniae* Eradication、*Escherichia coli* Eradication、Enterobacter aerogenes Eradication、Serious adverse events、adverse events、
Germany	221	RCT, 2 arms	111	65.7 ± 13.8	30%%	Imipenem–cilastatin	1 g q8h	13.3 ± 4.3	110	68.4 ± 13.7	42.30%	13.5 ± 4.2	Piperacillin-tazobactam	4.5 g q8h	cure、clinical failure、mortality、adverse event、serious adverse events
USA	429	RCT, 2 arms	217	57.5	26.90%	Doripenem	0.5gq8h		212	59.3	37.80%		Piperacillin-tazobactam	4.5 g q6h	Clinical cure、all-cause mortality、adverse event、Serious adverse event、microbiological responses、
Spain	808	RCT, 2 arms	403	61·9	26%	Meropenem	1 g q8h	14.9	405	62.1	25%%	14·5	Ceftazidime-avibactam	2.5 g q8h	Clinical cure、all-cause mortality、adverse event、Serious adverse event、*Pseudomonas aeruginosa* clinical cure、*Klebsiella pneumoniae* clinical cure、*Enterobacter cloacae* clinical cure、*Escherichia coli* clinical cure、*Serratia marcescens* clinical cure
USA	726	RCT, 2arms	364	59·5	30.00%	Meropenem	1 g q8h	17·4	362	60·5	28.00%	17·5	Ceftolozane–tazobactam	3 g q8h	mortality、Clinical cure、Microbiological eradication、*Pseudomonas aeruginosa* clinical cure、Gram-negative pathogens (G-)、adverse event、Serious adverse event、Enterobacteriaceae、ESBL+
USA	531	RCT, 2 arms	264	60.5	32.60%	Imipenem + REL	1.25 g q6h	14.6	267	58.8	29%	14.8	Piperacillin-tazobactam,	4.5 g q6h	mortality、clinical response、microbiologic response、The incidence of relapse/clinical failure、adverse event、Serious adverse event、Discontinued drug due to AE、

3. Results

We searched CENTRAL, PubMed, and Embase and identified 1138 references. After primary screening and removal of duplicates, we excluded 857 articles. We analyzed the full-texts of 28 articles. Six articles were excluded due to incomplete data; one was a single-arm study; 12 were conference abstracts; one used different control drugs; one was not written in English or Chinese. The reasons for article exclusion are given in Fig. 1. Seven RCTs were selected for review and meta-analysis.

A total of 1653 patients with HAP were treated with carbapenems and 1653 patients were treated with BLBLIs. The main characteristics of cases are shown in Table 1. All studies reported mortality and the clinical response. Five studies reported on the microbiologic response. Six articles reported on AEs and SAEs.

The Cochrane Risk of Bias assessment tool was used to evaluate the quality of included studies. The outcomes of the risk of bias are summarized in Fig. 2. Seven studies had a very low risk for sequence generation. Joshi and colleagues [18] and Rea-Neto and co-workers [19] did not mention if allocation concealment was conducted. Four studies supported by a commercial company carried a high risk of performance bias.

3.1. Mortality

ACM was reported in seven articles. Four articles reported 28-day mortality [15,16,20,22]. Twenty-one-day mortality was documented in two studies [18,20]. One study did not report on the time of death [17].

There was no significant difference in ACM, and low heterogeneity was noted between carbapenems groups *versus* BLBLIs (RR = 0.88, 95%CI = 0.75–1.03, I^2 = 0%, P = 0.11, high certainty) (Fig. 3). The results of the sensitivity analysis showed that excluding a single study did not have an impact on the final outcome (Table 2).

We conducted a subgroup analysis of mortality according to the type of carbapenems. There was no significant difference between carbapenems *versus* BLBLIs (RR = 0.72, 95%CI = 0.47–1.10, I^2 = 0%, P = 0.13) (Fig. 4). Similar results were observed for meropenem *versus* ceftazidime–avibactam and ceftolozane–tazobactam (RR = 0.93, 95%CI = 0.67–1.30, I^2 = 42%, P = 0.68) (Fig. 4).

3.2. Clinical response

3.2.1. Clinical cure

The prevalence of clinical cure was reported in seven studies. There was no significant difference in the prevalence of clinical cure with low heterogeneity between carbapenems groups *versus* BLBLIs groups (RR = 1.02, 95%CI = 0.96–1.09, I^2 = 30%, P = 0.49, high certainty) (Fig. 5). Two studies reported the clinical response at an early follow-up visit (7–14 days) [16,21]; Joshi and colleagues [18] reported a test-of-cure assessment at 14±7days. Schmitt and coworkers [20] reported the clinical response on the final day of treatment, day-21. Réa-Neto et al. [19] reported a test-of-cure visit conducted at 6–20 days. Torres and colleagues [15] reported a test-of-cure visit on days 21–25.

3.2.2. Clinical failure

Clinical failure was reported in six studies [16–21]. There were 153/906 patients (16.9%) in the carbapenems group and 125/888 patients (14.1%) in the BLBLIs group. Joshi et al. [18] reported clinical failure due to *Staphylococcus aureus*, *Klebsiella pneumoniae,* or *Klebsiella aerogenes* infections, but comparable data for clinical failure were not available from the other included studies. Two studies reported clinical failure due to *P. aeruginosa* infection [17,18]. Clinical failure was observed with carbapenems groups *versus* BLBLIs groups but the difference was not significant (RR = 1.19, 95%CI = 0.97–1.47, I^2 = 0%, P = 0.10, moderate certainty) and with low heterogeneity (Fig. 6).
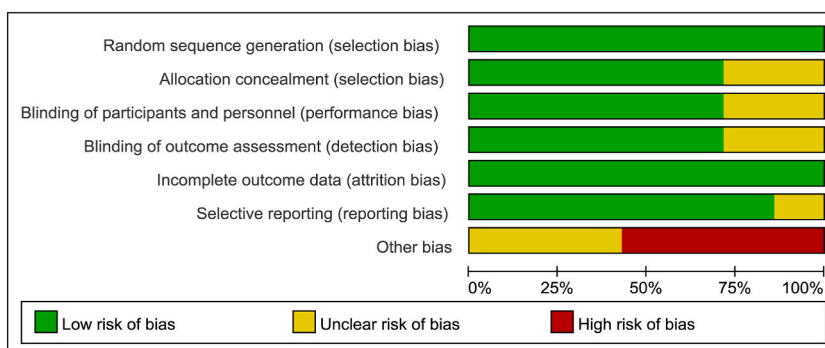

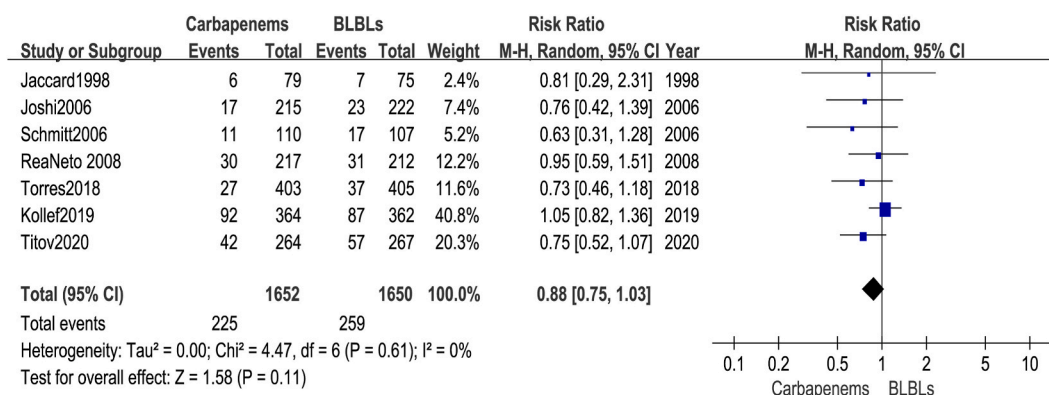**Fig. 2.** Assessment of risk of bias.

Study or Subgroup	Carbapenems Events	Total	BLBLs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Jaccard1998	6	79	7	75	2.4%	0.81 [0.29, 2.31]	1998
Joshi2006	17	215	23	222	7.4%	0.76 [0.42, 1.39]	2006
Schmitt2006	11	110	17	107	5.2%	0.63 [0.31, 1.28]	2006
ReaNeto 2008	30	217	31	212	12.2%	0.95 [0.59, 1.51]	2008
Torres2018	27	403	37	405	11.6%	0.73 [0.46, 1.18]	2018
Kollef2019	92	364	87	362	40.8%	1.05 [0.82, 1.36]	2019
Titov2020	42	264	57	267	20.3%	0.75 [0.52, 1.07]	2020
Total (95% CI)		**1652**		**1650**	**100.0%**	**0.88 [0.75, 1.03]**	
Total events	225		259				

Heterogeneity: Tau² = 0.00; Chi² = 4.47, df = 6 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.58 (P = 0.11)

Fig. 3. All-cause mortality between carbapenems versus BLBLIs for the treatment of nosocomial pneumonia.

Table 2
Sensitivity analyses (omission of a single RCT) *.

	Mortality (95%CI)	P
All studies	0.88 (0.75–1.03)	0.11
selected study omitted		
Jaccard, 1998	0.96 (0.75–1.22)	0.72
Joshi, 2006	0.98 (0.76–1.25)	0.86
Schmitt, 2006	0.99 (0.79–1.24)	0.95
Rea-Neto, 2008	0.95 (0.72–1.24)	0.69
Torres, 2018	0.90 (0.71–1.14)	0.39
Kollef, 2019	0.87 (0.71–1.08)	0.2
Titov, 2020	1.04 (0.83–1.3)	0.73

3.3. Microbiologic clinical cure rates

Five studies reported the microbiologic clinical cure rates [15,16,18,19,21]. There was no significant difference between carbapenems groups *versus* BLBLIs groups (RR = 0.98, 95%CI = 0.89–1.06, I² = 40%, P = 0.57, moderate certainty) and with moderate heterogeneity (Fig. 7) We conducted a subgroup analysis based on the classification of microorganisms. Four studies reported on clinical cure after *P. aeruginosa* infection [15–18]. There was no significant difference between carbapenems groups *versus* BLBLIs groups (RR = 1.16, 95%CI = 0.87–1.53, I² = 49%, P = 0.31) and with moderate heterogeneity (Fig. 7). Two studies [15,18] reported on *K. pneumoniae* eradication but there was no significant difference between carbapenems groups *versus* BLBLI groups (RR = 1.24, 95%CI = 0.77–2.0, I² = 60%, P = 0.37) and with moderate heterogeneity (Fig. 7). Similar results were observed for *Escherichia coli* eradication [15,18] between carbapenems groups *versus* BLBLIs groups (RR = 0.99, 95%CI = 0.8–1.24, I² = 0%, P = 0.95) and with low heterogeneity (Fig. 7).

3.4. Resistance by P. aeruginosa

Three studies reported resistance by *P. aeruginosa* to antibiotic treatment [16–18]. There was no significant difference between carbapenem groups *versus* BLBLIs groups (RR = 2.43, 95%CI = 0.86–6.81, I² = 49%, P = 0.09, low certainty) and with moderate heterogeneity (Fig. 8).

3.5. Side-effects of antibiotic treatment

3.5.1. AEs

Six studies reported AEs [15,16,18,21]. There was no significant difference in AEs between carbapenems groups *versus* BLBLIs groups (RR = 0.98, 95%CI = 0.93–1.02, I² = 0%, P = 0.31, high certainty) and with low heterogeneity Table 4). We conducted subgroup analyses based on the categorization of AEs. Three studies reported on the prevalence of diarrhea, but a significant difference between carbapenems groups *versus* BLBLIs groups was not observed (RR = 0.89, 95%CI = 0.66–1.21, I² = 26%, P = 0.47) (Supplementary Table 4). The prevalence of vomiting was reported in three studies and discovered that no significant difference between carbapenems groups *versus* BLBLIs groups (RR = 1.19, 95%CI = 0.84–1.71, I² = 0%, P = 0.33) (Table 4). Two studies reported on the prevalence of rash and discovered that no significant difference between carbapenems groups *versus* BLBLIs groups (RR = 0.98, 95%CI = 0.66–1.45, I² = 0%, P = 0.92) (Table 4). Three studies reported on the prevalence of thrombocythemia and discovered that no significant difference between carbapenems groups *versus* BLBLIs groups (RR = 0.65, 95%CI = 0.38–1.10, I² = 0%, P = 0.11) (Table 4).

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Table 3
GRADE assessments of evidence.

| Category	No.RCT comparisons	Dowagrade quality of evidence					Upgrade quality of evidence			Overall quality of evidence
		Risk of bias	Inconsistency	Indirectness	Imprecison	Publication Bias	Dose-response	Large Effect	Plausible Confounding	
mortality	7	not serious	not serious	not serious	not serious	not serious	No	No	No	⊕⊕⊕⊕ High
clinical cure	7	not serious	not serious	not serious	not serious	not serious	No	No	No	⊕⊕⊕⊕ High
clinical failure	6	not serious	not serious	not serious	serious	not serious	No	No	No	⊕⊕⊕○ Moderate
microbiologic clinical cure	6	not serious	not serious	not serious	not serious	not serious	No	No	No	⊕⊕⊕⊕ High
P.aeruginosa resistance	3	not serious	not serious	not serious	very serious	not serious	No	No	No	⊕⊕○○ Low
AES	6	not serious	not serious	not serious	not serious	not serious	No	No	No	⊕⊕⊕⊕ High
SAEs	4	not serious	not serious	not serious	not serious	not serious	No	No	No	⊕⊕⊕⊕ High
events leading to study discontinuation	3	not serious	not serious	not serious	not serious	not serious	No	No	No	⊕⊕⊕⊕ High
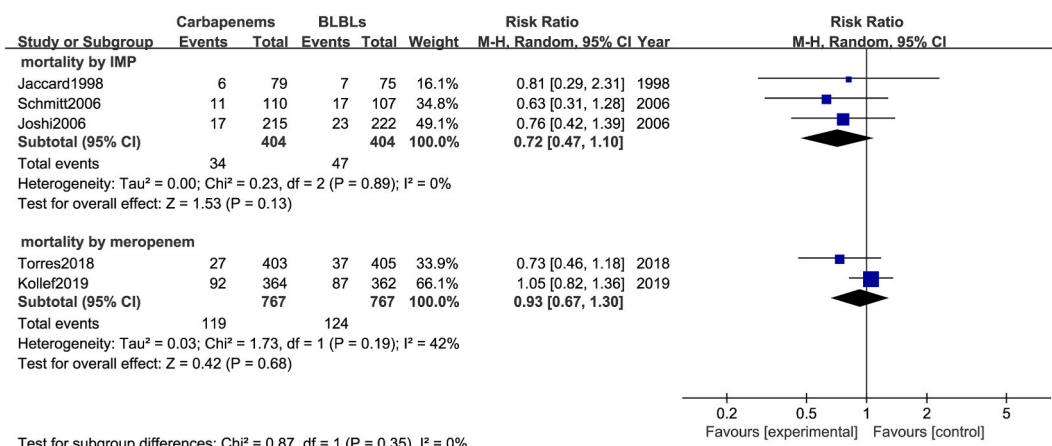
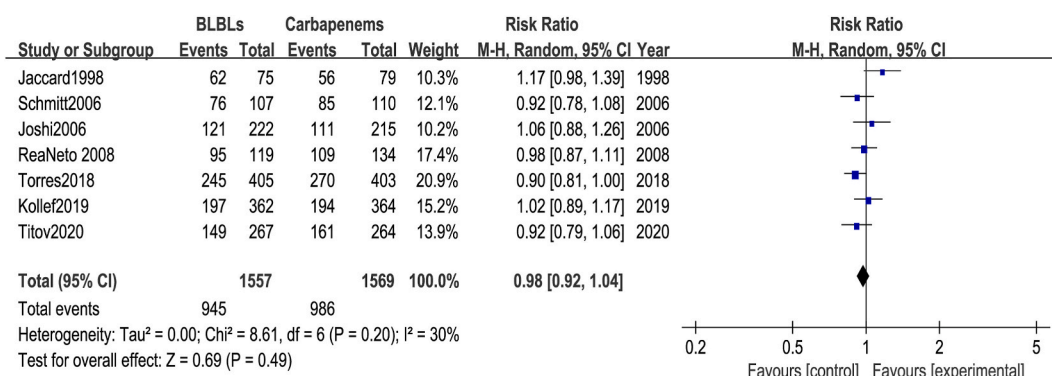**Fig. 4.** All-cause mortality according to the type of carbapenems.

Fig. 5. Clinical cure between carbapenems versus BLBLIs for the treatment of nosocomial pneumonia.
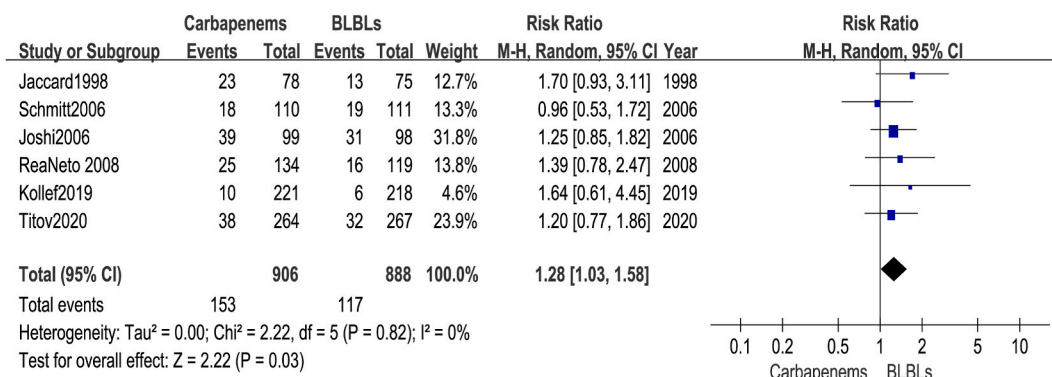

Fig. 6. Clinical failure between carbapenems versus BLBLIs for the treatment of nosocomial pneumonia.

3.5.2. SAEs

Four studies reported SAEs [15,16,19,21] but a significant difference between carbapenems groups *versus* BLBLIs groups was not found (RR = 0.83, 95%CI = 0.73–0.94, $I^2 = 0$%, P = 0.004, high certainty) and with low heterogeneity (Table 4). Torres and colleagues [15] reported SAEs of infections and infestations of respiratory, thoracic, and mediastinal areas, and cardiac disorders. Kollef and coworkers [16] reported the most common fatal SAEs to be multiple-organ failure, septic shock, brain edema, and acute cardiac failure.

3.5.3. Events leading to study discontinuation

Three studies reported on events leading to study discontinuation [15,16,21], but a significant difference between carbapenems
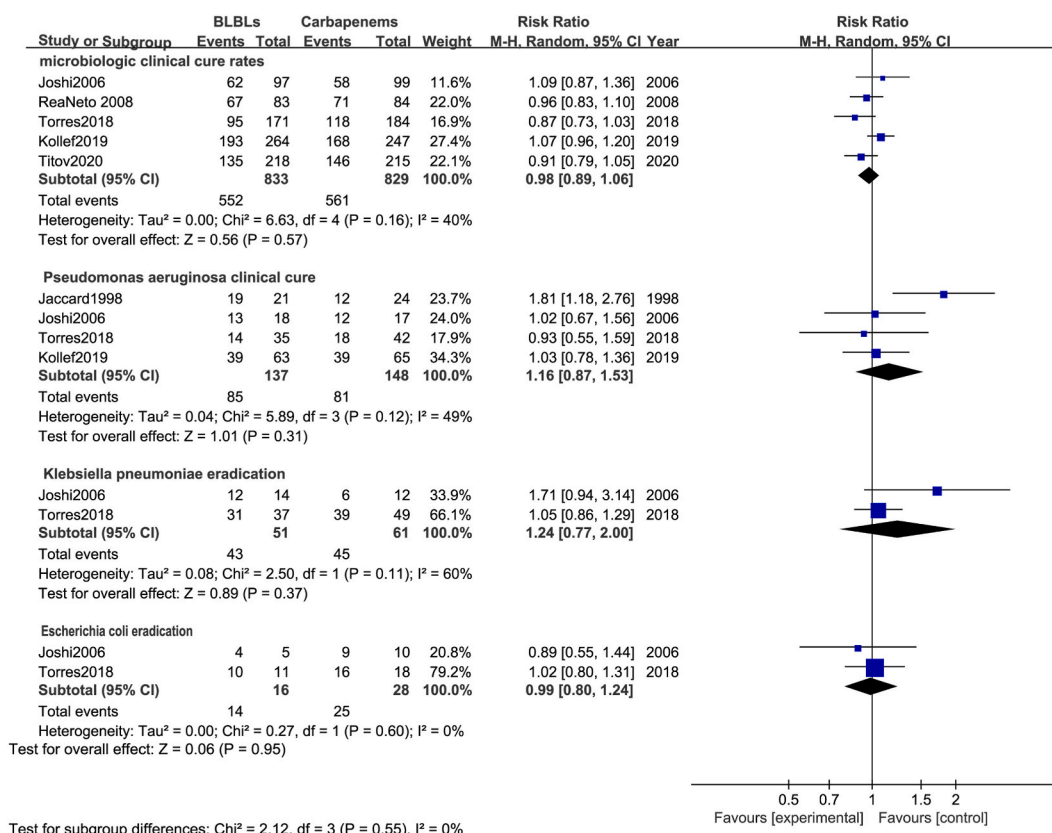
Fig. 7. Microbiologic clinical cure rates between carbapenems versus BLBLIs for the treatment of nosocomial pneumonia.
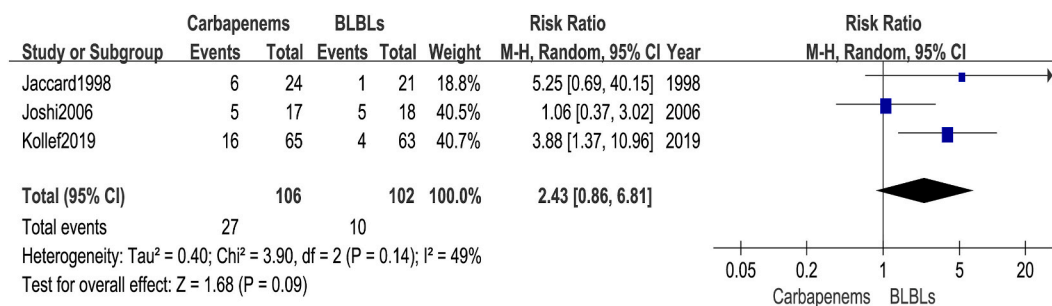

Fig. 8. Resistance by *P. aeruginosa* between carbapenems versus BLBLIs for the treatment of nosocomial pneumonia.

Table 4
Side-effects.

	RR	95%CI	I^2	P
Adverse event	0.98	0.93–1.02	0%	0.31
Diarrhea	0.89	0.66–1.21	26%	0.47
Vomiting	1.9	0.84–1.71	0%	0.33
Rash	0.98	0.66–1.45	0%	0.92
Thrombocythemia	0.65	0.38–1.10	0%	0.11
Severe adverse event	0.83	0.73–0.94	0%	0.004
leading to study drug discontinuation	0.9	0.63–1.29	16%	0.57

groups *versus* BLBLIs groups was not observed (RR = 0.90, 95%CI = 0.63–1.29, I^2 = 16%, P = 0.57, high certainty) and with low heterogeneity (Table 4).

4. Discussion

In this meta-analysis, we found no significant difference in the prevalence of mortality, clinical cure, clinical failure, or the microbiologic response in patients treated with carbapenems or BLBLIs. Similar results were observed with regard to AEs. However, we found that patients treated with carbapenems may suffer resistance to *P. aeruginosa* but no significant difference between carbapenems groups *versus* BLBLIs groups. Patients treated with carbapenems were less likely to experience SAEs than patients treated with BLBLIs.

Systematic reviews and meta-analyses have compared carbapenems *versus* β-lactams antibiotics, but not BLBLIs. Subgroup analysis for the specific type of carbapenems and pathogen has yet to be performed. Tiempos et al. reported use of carbapenems to be associated with a lower risk of death than that using fluoroquinolones or β-lactams but the methodological quality of that study was low. However, if RCTs with a modified Jadad score of 3 were excluded from their analysis, there would be no significant difference in mortality between patients using carbapenems, fluoroquinolones, or β-lactams. Tiempos et al. included only two studies comparing IMI *versus* TZP. They also reported use of carbapenems to be associated with a higher prevalence of clinical failure in patients with pneumonia due to *P. aeruginosa* infection [22]. Aarts et al. identified 41 clinical trials comparing 29 unique regimens against VAP. They found no differences in the risk of death between any of the regimens employed. Only ceftazidime combined with an aminoglycoside was inferior to meropenem [23].

We included seven studies looking at use of carbapenems and BLBLIs. We conducted a sensitivity analysis on mortality, and the result was stable. We conducted a subgroup analysis of mortality and found no difference between IMI *versus* TZP and meropenem *versus* a novel BLBLIs. A Cochrane systematic review by Arthur and colleagues reported no difference in ACM for VAP between carbapenem and non-carbapenem therapies. They found the use of carbapenems to be associated with a significant increase in the prevalence of clinical cure, but they included three studies with a total of 598 patients with VAP. Their results were limited by wide confidence intervals [24]. We included seven studies with 3306 patients with HAP or VAP, which may account for the difference in results. Donnell et al. found no differences in the prevalence of clinical failure or mortality between carbapenems *versus* alternative *β*-lactams (cefepime or TZP) for treatment of nosocomial pneumonia. They included five studies (1274 patients) but subgroup analyses revealed that patients treated with imipenem experienced clinical failure in pneumonia caused by *P. aeruginosa* infection. The result was observed in two studies (64 patients) and was limited by wide confidence intervals. Donnell et al. also found that patients infected with *P. aeruginosa* were more likely to develop resistance compared with those administered TZP or cefepime. The result was observed in three studies (132 patients) and was limited by a wide confidence interval [25]. Concerning clinical failure, we included six studies (1795 patients) with narrow confidence and low heterogeneity between carbapenems *versus* BLBLIs. Howatt et al. found no significant difference in the prevalence of the clinical response except in non-carbapenem groups with a low proportion of VAP. They observed a trend towards increasing antimicrobial resistance in the carbapenem group. They included six studies, but only one study had a comparator regimen to TZP [26]. With respect to *P. aeruginosa* resistance, we included three studies (208 patients) with narrow 95%CIs between carbapenems *versus* BLBLIs.

We observed a trend of resistance development when looking at *P. aeruginosa* infection but no significant difference between carbapenems groups *versus* BLBLIs groups. Carbapenems are the last line of defense for treatment of severe Gram-negative infections. The prevalence of drug resistance has increased gradually in recent years, and even produced carbapenem-resistant enterobacteriaceae (CRE) [27]. CRE is associated with significant morbidity and mortality [28]. MDR Gram-negative bacteria have been reported to account for 70% of hospital-acquired infections [29]. Carbapenem-resistant *K. pneumoniae* is caused predominantly by the production of carbapenems that also affect most other β-lactam antibiotics [30]. A recent study showed that carbapenem use is associated with an increased risk of cross-colonization by MDR *K. pneumoniae* strains [31].

Antibiotic concentrations in epithelial lining fluid (ELF) are important clinical parameters for activity against extracellular pathogens. The maximal bactericidal activity for meropenem is approximately the fraction of the dosing interval when free plasma concentrations are above a minimum inhibitory concentration (fT > MIC) of 40%–50%. Critically ill patients with HAP require a higher pharmacodynamic target of 50%–100% for fT > MIC. If the meropenem dose is 1 g/8 h, the probability of target attainment could be achieved for isolates with a MIC <2 mg. L^{-1} [32]. Administration of doripenem (500 mg/8 h) could lead to doripenem concentrations in the ELF <1 μg mL^{-1}. These lower doripenem concentrations in ELF may lead to a lower prevalence of clinical cure and an increased risk of death [33,34]. A recent study showed that exposure to imipenem in ELF was 44% in healthy volunteers [35].

A multivariable analysis showed that previous carbapenem use was associated independently with extensively drug-resistant (XDR-PA) infections [30]. There was a trend towards an increased duration of hospital stay if MIC ≥4 mg. L^{-1} [36]. Even with prolonged infusion schemes, achieving optimal outcomes for patients with increased MICs may not be possible. Antibiotic exposure increases the acquisition of highly resistant *Acinetobacter baumannii* and *P. aeruginosa*, so use of appropriate antibiotics is imperative. To reduce the emergence of drug resistance, sufficient doses of carbapenems should be given to kill sensitive bacteria and prevent drug-resistant bacteria.

Given the research evidence, physicians should be cautious when choosing carbapenems as first-line therapy for treating nosocomial pneumonia. An Infectious Diseases Society of America guideline published in 2016 stated that carbapenems may not be suitable for many intensive care unit (ICU) patients with HAP because resistance to carbapenems is rising [2]. Several studies have identified administration of carbapenems to be an independent risk factor for the emergence of carbapenem-resistant Gram-negative bacteria in hospital [37,38]. In this scenario, a strategy to minimize the emergence of resistance to carbapenems is administration to achieve sufficient drug exposure to kill susceptible bacteria and prevent the emergence of resistant subpopulations [39,40]. Optimization of

carbapenem use may be a reasonable measure of antimicrobial resistance. The measure includes carbapenem discontinuation, change to a narrower-spectrum antibiotic, dose optimization, or alternative therapy [36,41]. A recent review showed that drug degradation was well tolerated in ICU patients with HAP, and had no effect on antimicrobial resistance [42]. Garcinuno and colleagues showed that carbapenems should be the first choice for severe infections but that alternatives should be used in mild and moderate infections with HAP [43]. Adela et al. estimated the dose needed for isolates with intermediate susceptibility (MIC between 2 and ≤8 mg/L) was as high as 8 g/8 h, which is four-times higher than the maximum licensed meropenem dose [44].

In terms of safety, common AEs were gastrointestinal symptoms (nausea, vomiting, and diarrhea) and thrombocythemia. We found no significant difference between carbapenems and BLIs in terms of AEs. However, BLBLIs elicited fewer SAEs than carbapenems. The most common SAEs were infections (respiratory, thoracic), mediastinal disorders, and cardiac disorders [13].

Our meta-analysis had some limitations. First, some studies did not report information about allocation concealment. Second, only two studies reported clinical cure rates according to the Acute Physiology and Chronic Health Evaluation (APACHE) category but with different scoring ranges, so the subgroup analysis based on APACHE category could not be conducted. Third, only three studies focused on *P. aeruginosa* resistance included in our meta-analysis. Two studies reported on *P. aeruginosa* resistance with IMI and only one study reported on *P. aeruginosa* resistance with meropenem. Finally, the language of the studies was limited to English or Chinese, which resulted in a language bias.

5. Conclusion

Treatment of HAP/VAP with carbapenems may increase the chance of *P. aeruginosa* resistance. Conventional doses of carbapenems may not be suitable for treating patients with HAP. The dose of carbapenems was optimized according to the MIC of patients, and carbapenems could be administered by prolonged infusion and at a high dose. Ceftazidime–avibactam and ceftolozane–tazobactam were suitable treatment options for patients with nosocomial pneumonia caused by *P. aeruginosa*, Enterobacteriaceae, or other Gram-negative pathogens residing in the lower respiratory tract. However, novel BLBLIs are expensive, would add to the financial burden of patients, and increase the risk of SAEs.

Author contribution statement

Huaiqin Cang, Jing Li: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Xianghua Quan: Performed the experiments; Contributed reagents, materials, analysis tools or data. Yu Liang, Xue Yang, Xianghua Chu: Contributed reagents, materials, analysis tools or data.

Data availability statement

Data included in article/supp. Material/referenced in article.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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