Systematic Review and Meta-Analysis

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Efficacy and safety of cefoperazone-sulbactam in empiric therapy for febrile neutropenia

A systemic review and meta-analysis

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Abstract

Purpose: This meta-analysis assessed the clinical efficacy and safety of cefoperazone-sulbactam for empiric therapy febrile neutropenia.

Methods: The PubMed, Web of Science, EBSCO, Cochrane Library, Ovid Medline, EMBASE, and ClinicalTrial.gov database were searched through May 10, 2019. Only clinical trials comparing cefoperazone-sulbactam with other antibiotics for empiric treatment of febrile neutropenia were included. The primary outcome was treatment success without modification, and the secondary outcomes were all-cause mortality and adverse events (AEs).

Results: Ten randomized controlled trials (RCTs) and 1 retrospective cohort study were included. Overall, cefoperazone-sulbactam exhibited a treatment success rate similar to those of comparator drugs for the treatment of febrile neutropenia (odds ratio [OR], 1.03; 95% confidence interval [CI], 0.85 to 1.24, $I^2=0\%$). A similar finding was noted in pooled analysis of 10 RCTs (OR, 1.07; 95% CI, 0.88 to 1.30, $I^2=0\%$). Subgroup analysis showed that cefoperazone-sulbactam had a treatment success rate similar to the rates of comparators for adults (OR, 1.10; 95% CI, 0.88 to 1.38, $I^2=0\%$) and children (OR, 0.96; 95% CI, 0.63 to 1.46, $I^2=0\%$). Cefoperazone-sulbactam did not differ significantly from comparators in the risks of all-cause mortality (OR, 0.96; 95% CI, 0.58 to 1.58, $I^2=0\%$) or common AEs, namely rash, nausea/vomiting, and superinfection.

Conclusion: The clinical efficacy and tolerability of cefoperazone-sulbactam are comparable to those of comparator drugs in the treatment of febrile neutropenia.

Abbreviations: AE = adverse event, CI = confidence interval, MRSA = methicillin-resistant *Staphylococcus aureus*, OR = odds ratio, RCT = randomized controlled trial.

Keywords: cefoperazone-sulbactam, efficacy, febrile neutropenia, mortality

1. Introduction

Febrile neutropenia is defined as the development of a fever during a period of significant neutropenia.[1] Despite improvements in cancer management, febrile neutropenia remains a severe complication for patients undergoing chemotherapy for cancer; approximately 1% of patients receiving chemotherapy develop febrile neutropenia.[2] Febrile neutropenia is associated with morbidity and mortality.[2] Patients with febrile neutropenia should be administered empiric antimicrobial agents intravenously; currently, broad-spectrum antibiotics such as antipseudomonal beta-lactam, carbapenems, and piperacillin-tazobactam are recommended.[3,4]

Cefoperazone-sulbactam is a broad-spectrum antibiotic and approved for the treatment of several acute bacterial infections. Even for multidrug-resistant organisms, such as extended-spectrum β-lactamase–producing Enterobacteriaceae and carbapenem-resistant *Acinetobacter baumannii*, cefoperazone-sulbactam exhibits potent in vitro activity that is unaffected by inoculum effects.[5–7] Therefore, cefoperazone-sulbactam can be considered a therapeutic option for febrile neutropenia. Several clinical studies[8–17] have investigated the efficacy and safety of cefoperazone-sulbactam for the treatment of febrile neutropenia. However, no meta-analysis has compared the efficacy and safety of cefoperazone-sulbactam with those of other antibiotics commonly used for treating febrile neutropenia. Therefore, we conducted a comprehensive meta-analysis to provide high-quality evidence of the efficacy and safety of cefoperazone-sulbactam for treating febrile neutropenia.

2. Methods

2.1. Data sources and search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses when searching for articles, selecting

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studies, evaluating article quality, and analyzing data.[18] We searched for candidate articles published before May 10, 2019, on the PubMed, Web of Science, EBSCO, Cochrane Library, Ovid Medline, EMBASE, and ClinicalTrial.gov databases. The search terms were "febrile neutropenia," "cefoperazone," "sulbactam," "cefoperazone-sulbactam," "sulperazone," "neutropenic fever," "and "neutropenic sepsis." We applied no publication year or language limitations. The definitions of febrile neutropenia varied; the cutoff neutrophil counts per liter were either 500 or 1000, and the definitions of fever were either a single oral temperature of >38.3°C (101°F) or a temperature >38.0°C (100.4°F) sustained for >1 hour. We permitted simultaneous administration of granulocyte colony–stimulating factor and cefoperazone-sulbactam as well as the use of the same anti-MRSA drug or aminoglycoside in both the study and control groups. Three investigators reviewed the full texts of the candidate articles to finalize the experimental and control groups included for meta-analysis. Three investigators reviewed the study methods, site, duration, and population as well as the treatment regimen reported in the articles. Initially, 2 investigators (Lan and Chang) examined the publications independently to avoid bias, and the third author (Lu) resolved any disagreements. We recorded the year of publication; study design, duration, site, and population; antibiotic regimen of cefoperazone-sulbactam and comparators; outcomes; and adverse effects reported in the included studies.

2.2. Definitions and outcomes

The primary outcome was treatment success without modification of the initial antibiotic regimen. Although some researchers consider success with regimen modification as treatment successes, this was not the primary outcome of our meta-analysis. The secondary outcomes were all-cause mortality and adverse events (AEs).

2.3. Quality assessment and data analysis

The investigators used the Cochrane Collaboration criteria to assess the study designs methodological quality; quality of included randomized controlled trials (RCTs), and observation studies were evaluated using the Cochrane risk-of-bias tool and standardized critical appraisal instruments from the Joanna Briggs Institute, respectively. Differences in opinion among the investigators were resolved through discussion and voting. Meta-analysis (drug efficacy and safety) was conducted using Review Manager software (RevMan, 5.3; Cochrane Informatics & Knowledge Management Department). The heterogeneity of the studies was measured using the I^2 statistic and the Q test (heterogeneity X^2). A Q test result of $P < .1$ or $I^2 > 50\%$ indicates heterogeneity; in such cases, a random-effects model was used. In contrast, if heterogeneity was absent in a study, a fixed-effects model was used. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for outcome analyses.

3. Results

The search results yielded 90 records from the online databases (Appendix 1, http://links.lww.com/MD/D864); 57 were excluded because of duplication, 19 records were deemed irrelevant after the title and abstract were screened, and 3 records were deemed irrelevant after the full text was screened. Finally, 11 studies[8–17,19] were included in the meta-analysis (Fig. 1). The risk of bias for each RCT is shown in Figure 2.

3.1. Study characteristics and study quality

Ten prospective RCTs[8–15,17,19] and 1 retrospective cohort study[16] published between 1996 and 2018 met the inclusion criteria (Table 1). Except for 1 multicenter study,[13] all were conducted in a single center.[8,12,14–17,19] Six studies[8,10–12,14,16] were conducted in Turkey, 4 in the United States,[9,13,17,19] and

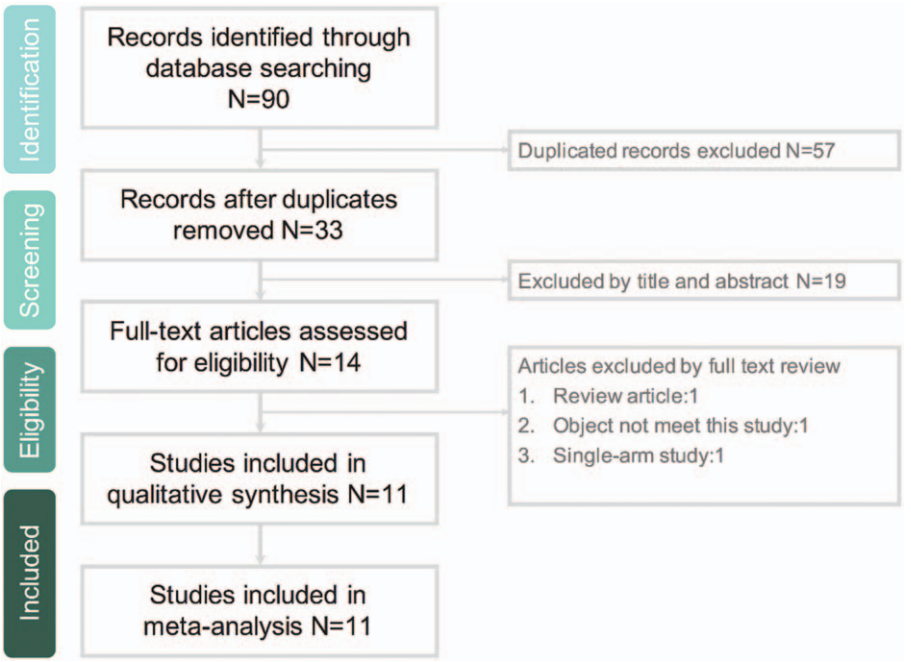

Figure 1. Flowchart of study selection process.

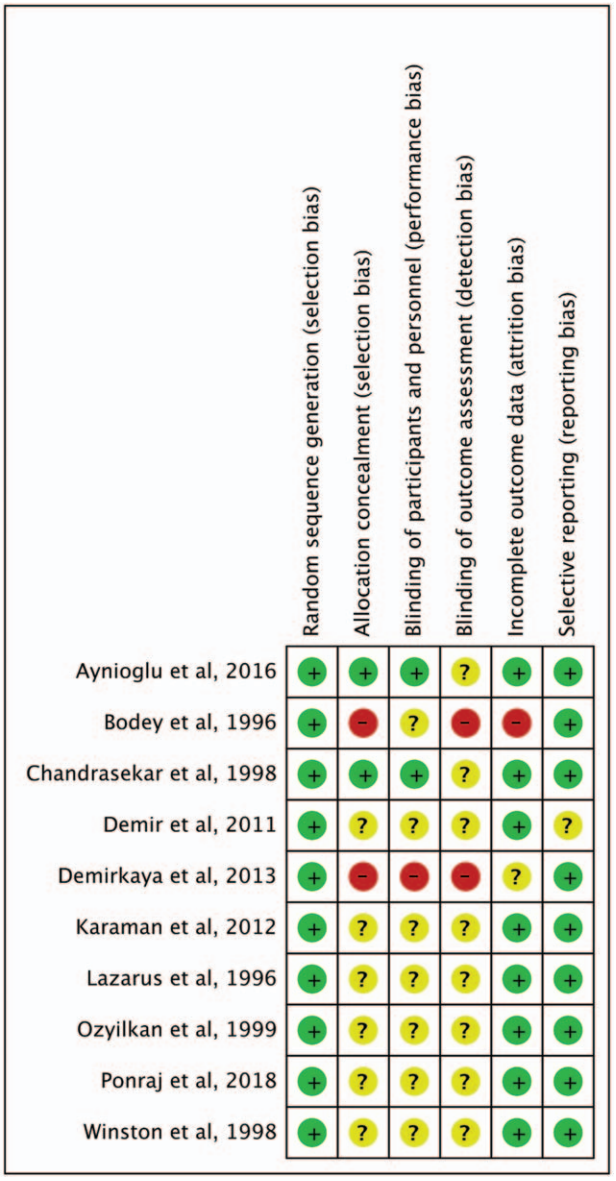

Figure 2. Risk of bias per study and domain of each RCT.

1 in India[15]; 3 focused on children,[10–12] and the other 8 involved mainly adults.[8,9,13–17,19] One study[13] focused on bone marrow transplant recipients; the other 10 involved patients with either solid or hematologic cancer.[8,12,14–17,19] Four studies[8,11,12,16] used piperacillin-tazobactam as the comparator, and 4 used carbapenems. One study each used cefepime,[15] cefoperazone plus mezlocillin,[13] and ceftazidime[19] as the comparator.

3.2. Treatment success without modification

Treatment success without modification was reported in all 11 studies,[8–17,19] which together comprise 2054 patients. Among 983 patients receiving cefoperazone-sulbactam, 565 (57.9%) achieved treatment success. Among 1071 patients receiving comparators, the treatment success rate was 56.9% ($n=609$). Cefoperazone-sulbactam had a treatment success rate similar to the comparators in empiric treatment of febrile neutropenia (OR, 1.03; 95% CI, 0.85 to 1.24, $I^2=0\%$, Fig. 3). In the pooled analysis of the 10 RCTs, no significant difference was found between cefoperazone-sulbactam and comparators (OR, 1.07; 95% CI, 0.88 to 1.30, $I^2=0\%$). The similarity between cefoperazone-sulbactam and comparators remained unchanged in the sensitivity test after individual studies were randomly excluded. No significant publication bias was found, according to a funnel plot (Fig. 4).

In the subgroup analysis by comparator, cefoperazone-sulbactam had a treatment success rate similar to those of piperacillin-tazobactam (OR, 0.95; 95% CI, 0.67 to 1.36, $I^2=0\%$) and carbapenems (OR, 1.25; 95% CI, 0.92 to 1.69, $I^2=0\%$). The pooled analysis of 7 studies[8,9,13,14,16,17,19] involving only adult patients revealed that cefoperazone-sulbactam had a treatment success rate therein similar to that of comparators (OR, 1.10; 95% CI, 0.88 to 1.38, $I^2=0\%$). The pooled analysis of 3 studies[10–12] involving only children also revealed a treatment success rate similar to that of comparators (OR, 0.96; 95% CI, 0.63 to 1.46, $I^2=0\%$). Moreover, this trend persisted despite changes in cefoperazone dosage (≥6 g/day, OR, 1.05; 95% CI, 0.79 to 1.39, $I^2=55.4\%$; 4 g/day, OR, 0.82; 95% CI, 0.39 to 1.72, $I^2=0\%$).

3.3. All-cause mortality

All-cause mortality was reported in 6 studies[8,10–12,15,16]; the mortality rate was 6.0% (31/520) and 6.5% (40/614) in patients receiving cefoperazone-sulbactam and those receiving comparators, respectively. No significant difference between cefoperazone-sulbactam and comparators in mortality was found through pooled analysis (OR, 0.96; 95% CI, 0.58 to 1.58, $I^2=0\%$, Fig. 5).

3.4. Adverse events

Among patients using cefoperazone-sulbactam, rash (10.1%, 71/703) was the most common AE, followed by nausea/vomiting (4.4%, 18/410). The risks of these 2 AEs were similar in the cefoperazone-sulbactam and comparator groups (rash, OR, 1.05; 95% CI, 0.71 to 1.53, $I^2=0\%$, nausea/vomiting, OR, 0.32; 95% CI, 0.03 to 3.74, $I^2=80\%$). In addition, pooled analysis revealed no significant difference in superinfection between the cefoperazone-sulbactam and comparator groups (OR, 0.73; 95% CI, 0.46 to 1.16, $I^2=0\%$). Prolongation of prothrombin time occurred in 10% (10/101) of patients receiving cefoperazone-sulbactam in one study[17]; however, no hemorrhage related to the study drug was observed.

4. Discussion

This meta-analysis of 11 clinical studies[8–17,19] determined that cefoperazone-sulbactam has a clinical efficacy similar to those of comparators in empiric treatment of febrile neutropenia. First, the success rate of cefoperazone in treating febrile neutropenia was similar to those of comparators in the pooled population of all 11 studies.[8–17,19] The similar clinical efficacy persisted in the analysis of only the 10 RCTs[8–15,17,19] and subsequent sensitivity test. Second, comparing cefoperazone-sulbactam with 2 antimicrobial agents, piperacillin-tazobactam and carbapenems, commonly recommended for the treatment of febrile neutropenia in subgroup analysis revealed no significant differences in the

Table 1

Characteristics of included studies.

Study, published year	Study design	Study period	Study site	Study populations
Bodey et al, 1996	Prospective, randomized, controlled trial	1990–1993	Single center in USA	Adult cancer patients with FN
Lazarus et al, 1996	Prospective, randomized, controlled trial	1989–1992	Multicenter in USA	Adult bone marrow transplant recipients with FN
Chandrasekar et al, 1998	Prospective, randomized, controlled trial	NA	Single center in USA	Adult (age ≥ 16 years) cancer patients with chemotherapy-associated neutropenia and fever
Winston et al, 1998	Prospective, randomized, controlled trial	NA	Single center in USA	FN adult (age ≥ 16 years)
Ozyilkan et al, 1999	Prospective, randomized, controlled trial	NA	Single center in Turkey	Adult patients with solid or hematological malignancy and FN
Demir et al, 2011	Prospective, randomized, controlled trial	2007–2009	Single center in Turkey	FN children (age≤16 years) hospitalized for lymphomas or solid tumors
Karaman et al, 2012	Prospective, randomized, controlled trial	2008–2009	Single center in Turkey	All patients 1–18 years of age treated for acute leukemia, lymphoma, or solid tumors with FN
Sipahi et al, 2013	Retrospective cohort study	2005–2011	Single center in Turkey	Low-risk FN
Demirkaya et al, 2013	Prospective, randomized, and open-label study	2009–2010	Single center in Turkey	0- to 18-year-old children with lymphoma or solid tumor who were hospitalized with FN
Aynioglu et al, 2016	Randomized, double-blind study	2010–2013	Single center in Turkey	Adult patients with hematological malignancies with FN
Ponraj et al, 2018	prospective, randomized, open-label study	2015–2016	Single center in India	Adult and pediatric patients with hematological or solid malignancies and high-risk FN

Study, published year	Episodes of patients		Mean or median age of patients		Dose regimen	
	CFP/SUL based	Comparator	CFP/SUL based	Comparator	CFP/SUL based	Comparator
Bodey et al, 1996	194	175	52	50	CFP/SUL (2 g q8 h) + vancomycin 1 g q12 h	Imipenem (500 mgq6 h) + vancomycin 1 g q12 h
Lazarus et al, 1996	66	66	41	41	CFP/SUL (2 g q12 h)	CFP 2 g q12h and mezlocillin 4g q6h
Chandrasekar et al, 1998	59	59	42	44	CFP/SUL (2 g q8h).	Ceftazidime 2g q8h
Winston et al, 1998	101	102	47	39	CFP/SUL (4 g q12 h)	Imipenem (500 mg q6 h)
Ozyilkan et al, 1999	15	15	41.6	49.6	CFP/SUL (2 g q12 h) plus AMK (15 mg/kg/day).	Imipenem (500 mg q6 h)
Demir et al, 2011	104	104	5.7	5.4	CFP/SUL 180 mg/kg/day	Imipenem, 60 mg/kg/day; meropenem 60 mg/kg/day
Karaman et al, 2012	50	52	5	4	CFP/SUL 100 mg/kg/day	PIP/TAZO 360 mg/kg/day.
Sipahi et al, 2013	59	113	50.6	54.1	CFP/SUL (2 g q8h)	PIP/TAZO (4.5 g q6h)
Demirkaya et al, 2013	57	59	5.5	7.0	CFP/SUL 100 mg/kg/day + AMK 15 mg/kg/day	PIP/TAZO 360 mg/kg/day + amikacin 15 mg/kg/day
Aynioglu et al, 2016	82	118	46	48	CFP/SUL (2 g q8h).	PIP/TAZO (4.5 g q6 h)
Ponraj et al, 2018	168	168	18.0	19.9	CFP/SUL (2 g q8h for adults and 50 mg/kg/ 8 h for children) + AMK 15 mg/kg daily	cefepime (2 g q8 h for adults and 50 mg/kg q8 h for children)

CFP/SUL = cefoperazone-sulbactam, CPF = cefoperazone, FN = febrile neutropenia, FN = febrile neutropenia, NA = not applicable, PIP/TAZO = piperacillin-tazobactam.

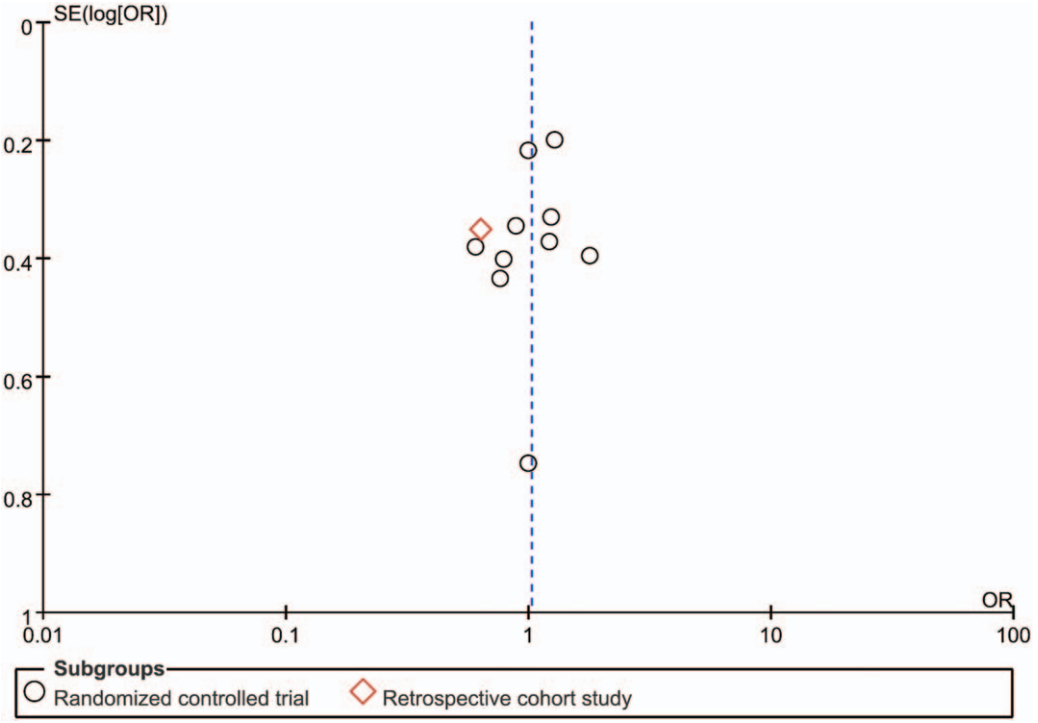

Figure 3. Funnel plot of overall clinical cure rates of cefoperazone-sulbactam and comparators in empiric treatment of febrile neutropenia.

clinical efficacy. Third, the treatment success rate of cefoperazone-sulbactam was similar to those of comparators in the pooled analyses of both pediatric and adult populations. Finally, the pooled all-cause mortality was only 6.0% among patients receiving cefoperazone-sulbactam, similar to that among patients receiving comparators. Overall, the findings suggest that cefoperazone-sulbactam can be as effective for the treatment of patients with febrile neutropenia as other available antibiotics.

In addition to the clinical response, AEs during antibiotic treatment are a concern in the management of patients with

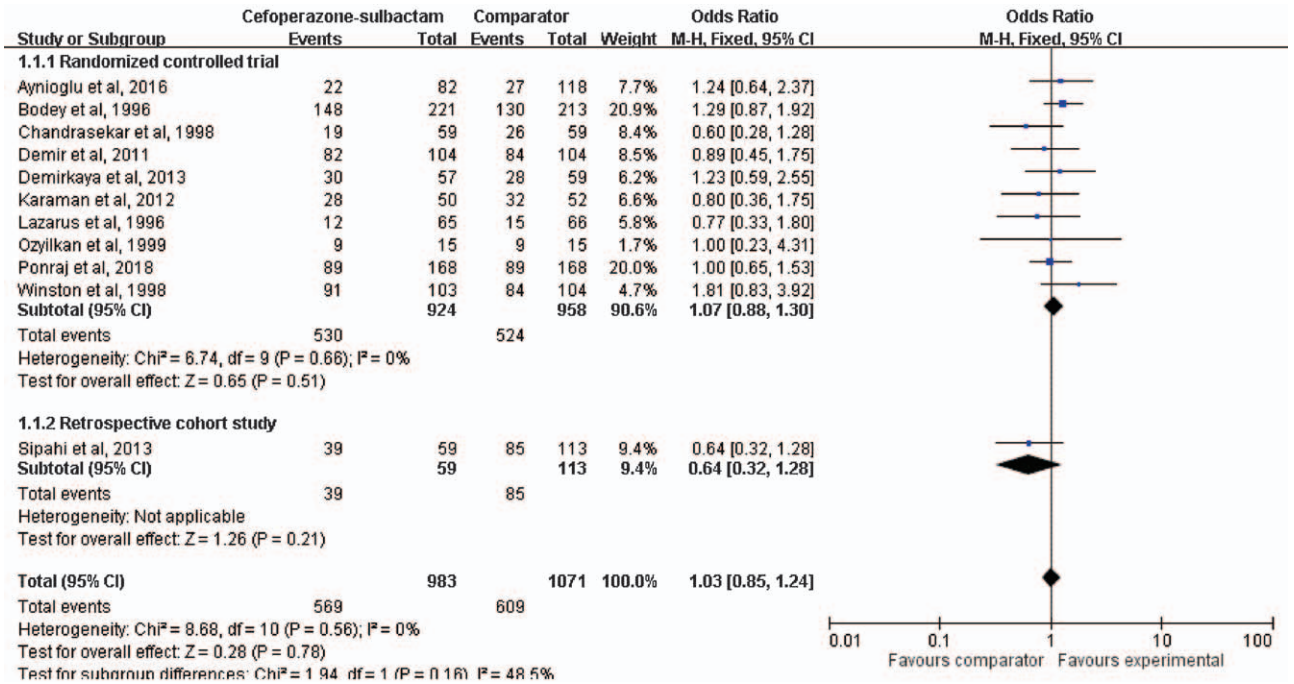

Figure 4. Forest plot for clinical cure rates of cefoperazone-sulbactam and comparators in empiric treatment of febrile neutropenia.

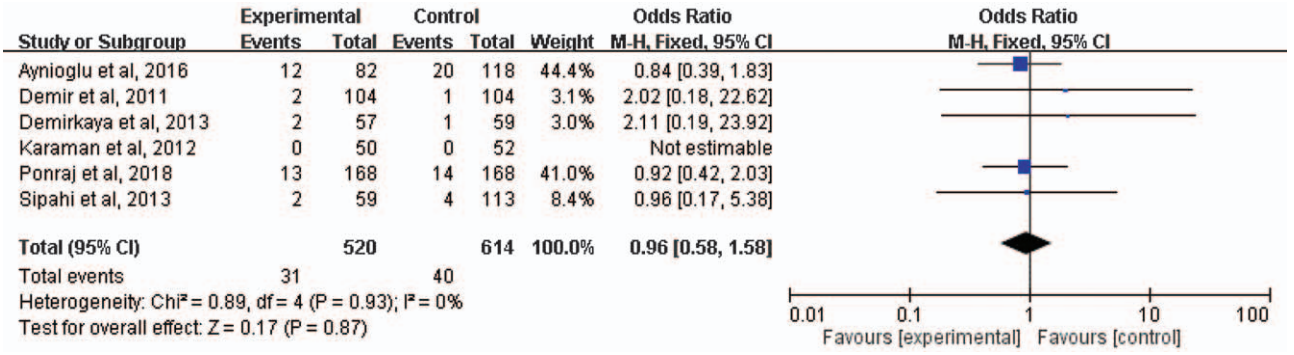

Figure 5. Forest plot of all-cause mortality rates of cefoperazone-sulbactam and comparators in treatment of febrile neutropenia.

febrile neutropenia. The most common AEs among patients receiving cefoperazone-sulbactam in this meta-analysis were rash and nausea/vomiting. The pooled risks of rash, nausea/vomiting, and superinfection were similar for cefoperazone-sulbactam and comparators. Another side effect of the study drug is the inhibition of vitamin K metabolism; such inhibition can induce abnormal coagulation and hemorrhage.[20,21] In this meta-analysis, only Winston et al[17] reported data relevant to this AE, reporting that the incidence of prolonged prothrombin time was 10%. However, no significant hemorrhage related to cefoperazone-sulbactam was noted in this report.[17] These findings suggest that cefoperazone is as safe as its comparators in the treatment of febrile neutropenia.

However, this meta-analysis has several limitations. First, we did not evaluate the efficacy of cefoperazone-sulbactam by sex, age, or underlying conditions, such as the type of cancer (eg., solid or hematologic) or risk of febrile neutropenia. Second, we did not assess the specific association between the in vitro activity and in vivo response of different microorganisms, particularly antibiotic-resistant ones, among patients with febrile neutropenia and documented microbial infection. Third, the numbers of studies and patients were low in this meta-analysis; therefore, a large-scale study is warranted to confirm our findings.

The findings of 11 clinical trials indicate that the efficacy and tolerability of cefoperazone-sulbactam are as high as those of its comparators for empiric treatment of patients with febrile neutropenia.

Author contributions

Conceptualization: Shao-Huan Lan, Chih-Cheng Lai, Hung-Jen Tang.
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Formal analysis: Shao-Huan Lan, Shen-Peng Chang, Li-Chin Lu, Hung-Jen Tang.
Investigation: Hung-Jen Tang.
Writing – original draft: Chih-Cheng Lai.
Writing – review & editing: Hung-Jen Tang.

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