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Review

Efficacy and safety of cefiderocol in the treatment of infections caused by Gram-negative bacteria: a systematic review and meta-analysis

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Abstract

Objective: To assess the efficacy and safety of cefiderocol (CFDC) in the treatment of Gram-negative bacteria (GNB) infections.

Methods: Relevant studies were collected from PubMed, Web of Science, Cochrane, and Embase databases, from inception to 15 October 2023. The search formula was as follow: "cefiderocol", "S-649266", "Gram-Negative Bacteria", "Gram Negative Bacteria", "*Klebsiella pneumoniae*", "*Hyalococcus pneumoniae*", and "*Bacterium pneumoniae* proposal". Stata 15.0 software was employed to pool data with risk ratios (RRs) and 95% confidence intervals (CIs). Data were pooled using a random- or a fixed-effects model.

Results: After a comprehensive study selection, 11 studies (5 RCTs and 7 observational studies) were retrieved that compared the efficacy of CFDC with other regimens, e.g., imipenem/cilastatin. The clinical response (RR = 1.00, 95% CI 0.94–1.08, I^2 = 0%) and microbiological response (RR = 0.95 95% CI = 0.80-1.14, I^2 = 68.7%) of CFDC were comparable to the control group. No significant differences were observed in mortality and adverse events. Furthermore, subgroup analyses showed that CFDC enhanced microbiological eradication in the follow-up group (RR = 1.25, 95% CI 1.05-1.49) and patients with complicated urinary tract infections (cUTI) (RR = 1.32, 95% CI 1.11- 1.57).

Conclusions: CFDC is a novel iron-carrying cephalosporin with the potential to effectively combat Gram-negative bacterial infections. Additional large and high-quality RCTs are required to further confirm the safety of CFDC.

Key words: Cefiderocol; meta-analysis; efficacy; safety; Gram-negative bacteria.

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Introduction

Gram-negative infections, caused by bacteria, such as *Klebsiella pneumonia* (Kpn), *Escherichia coli* (Eeo), and *Acinetobacter baumannii* (Aba), are becoming increasingly common and pose a serious threat to life by causing severe infections [1]. In addition, these bacteria are increasingly becoming resistant to drugs worldwide. The World Health Organization (WHO) estimates that around 10 million deaths per year will result from antimicrobial resistance by 2050, and the carbapenem-resistant *Acinetobacter baumannii* (CRAB) isolates raise great concern worldwide [2]. The US Centers for Disease Control and Prevention reported antibiotic resistance as an urgent threat, including identified carbapenem-resistant baumannii (CRAB) and carbapenem-resistant *Enterobacteriaceae* (CRE) [3]. As the primary drug, Carbapenem is usually used to treat serious Gram-negative infections, however, the emergence of multidrug-resistant bacteria diminishes the efficacy of existing antimicrobial drugs, posing significant challenges to clinical anti-infective treatment [4]. To combat infections by gram-negative bacilli with multidrug resistance, antibacterial agents with a broad spectrum are urgently required.

Cefiderocol (CFDC) is a novel siderophore cephalosporin, which inhibits the active efflux pump expression of Gram-negative bacteria (GNB) with stability against serine- and metallo-type carbapenemases [5,6]. Thus, it is effective in combating various Gram-negative infections. CFDC obtained approval from the US Food and Drug Administration in 2019 for treating adults with complex urinary tract infections (CUTIs), hospital-acquired pneumonia (HAP) caused by GNB, and ventilator-associated pneumonia [7]. Moreover, the drug also received approval from the European Medicines Agency for treating GNB infections in adults [8]. With its unique iron carrier mechanism against multidrug-resistant

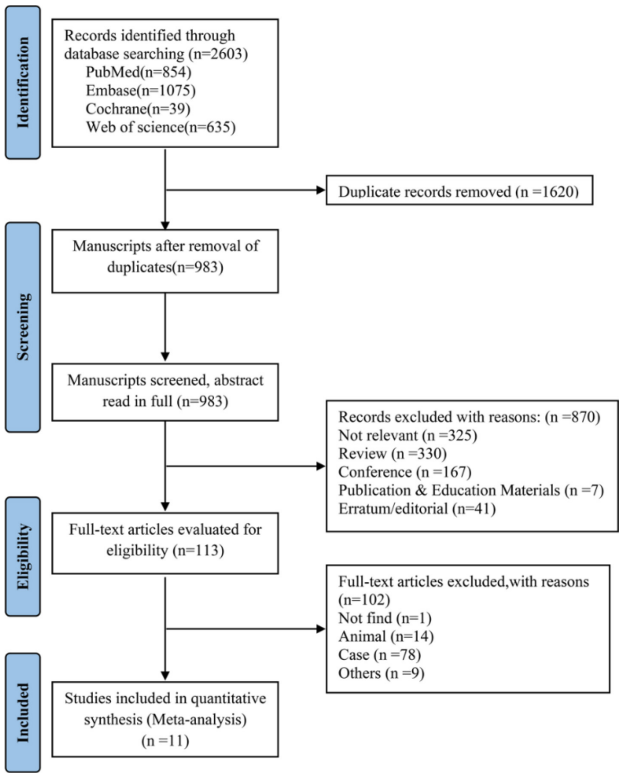
Gram-negative bacilli, CFDC is anticipated to emerge as a promising drug for infections caused by multidrug-resistant GNB [9,8].

A previous study reported that CFDC might be effective as an empirical treatment for severe GNB infections due to its favorable pharmacological profile [10]. However, no statistical analysis or quality validation was conducted. Likewise, most of the relevant literature was observational studies, case reports, and studies with small sample sizes. Recently, a meta-analysis study demonstrated the prospect of CFDC in the treatment of cUTI [11]. Although several case studies on RCTs have shown the impact of CFDC on infectious diseases [12-16], we still need systematically to understand their effects by combing literature (i.e. meta-analysis). Therefore, we conducted the meta-analysis for evaluating the efficacy and safety of this newly approved drug regimen.

Methods

This review study was carried out following the PRISMA guidelines [17] and the protocol was registered in the International Prospective Register of Systematic Reviews with prospero registration number: CRD42023424571.

Figure 1. PRISMA flow diagram of the study selection process.



Literature search

Relevant studies were collected from PubMed, Embase, Cochrane Library, and Web of Science from database inception to 15 October 2023, with language restriction to English. MeSH and keywords search terms included: "cefiderocol", "S-649266", "Gram-Negative Bacteria", "Gram Negative Bacteria", "*Klebsiella pneumoniae*", "Hyalococcus pneumoniae", "Klebsiella pneumoniae aerogenes", "*Bacillus pneumoniae*", "Bacterium pneumoniae proposal", "*Klebsiella rhinoscleromatis*", "*Acinetobacter baumanii*". The detailed search strategy is described in Supplementary Table 1.

Eligibility Criteria and Data Extraction

Inclusion criteria

(i) Study type: Published RCTs and prospective/retrospective observational studies on CFDC for treating GNB infections.

(ii) Study population: Patients with a confirmed diagnosis of common GNB infections such as cUTI, bloodstream infections (BSI), and HAP according to the currently accepted diagnostic basis; age, gender, and race were not restricted.

(iii) Interventions: Patients in the treatment group received CFDC, whereas patients in the control group were administered standard drugs such as meropenem/imipenem cilastatin/cefepime/doripenem/mitomycin/tigecycline; the dose and duration of treatment were unlimited in both groups.

(iv) Outcome indicators: clinical response, microbiological response, adverse events (AEs), serious adverse events (SAEs), and mortality.

Exclusion Criteria

(i) Studies with no outcome indicators, incorrect data, and incomplete data.

(ii) Summary reports of clinical trials.

(iii) In vitro antimicrobial studies, animal studies, pharmacokinetic studies, pharmacological studies, and reviews.

Study selection and data collection

EndNote version 20.1 was employed for data management and to remove duplicated articles. The title and abstract were assessed independently by 2 evaluators. After excluding duplicated studies, irrelevant studies, pharmacokinetic experiments, and in vitro inhibition experiments, the remaining studies were read comprehensively to identify eligible studies. In case of discrepancy, a third investigator was consulted

to discuss and resolve the issue. An extraction form was created to extract data, such as (1) basic information such as first author, year of publication, sample size, intervention, type of infection, a combination of drugs, duration of treatment, and microbial species; (2) data related to outcome indicators, clinical cure rates, and microbiological response rates prioritizing the use of modified intention-to-treat (mMITT) populations data at the end of the treatment trial (test of cure, TOC) or if not available, other data reported in the literature were used instead. AE incidence, SAE incidence, and mortality rates were used for the safety analysis population; (3) information on the quality of the included studies, including randomization methods, allocation concealment, blinding, data integrity, bias, etc.

Methodological Quality and Risk of Bias Assessment

The Cochrane Risk of Bias Tool was employed to assess the potential bias risk in the RCTs, involving the random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential biases [18]. Each study was assessed and classified as low, unclear, or high risk of bias using Review Manager 5.4. The Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) was employed to evaluate the observational studies [19]. The ROBINS-I comprises 7 domains and studies were judge as low, moderate, serious, or critical risk of bias under each domain. An open discussion would be conducted to resolve any disagreements between reviewers to reach a consensus.

Statistical analysis

Data were analyzed using Stata 15.0 (College Station, TX 77845 USA). Dichotomous data were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). Heterogeneity (I^2) value greater than 50% indicated statistically high heterogeneity. Dichotomous data were analyzed using either a fixed- or random-effects model, according to heterogeneity between studies. Sensitivity analysis was performed to examine the confidence in the outcomes. Egger's test was employed to evaluate the publication bias of the

Table 1. Characteristics of the included studies in the meta-analysis.

Author	Year	Design	Randomization	No. screened patients	Case load	Region	Treatment regime	Concomitant therapy	Comparator/dosage	Treatment duration, days	Infections	Pathogens	Outcomes
Richard G Wunderink	2020	Phase III, randomized, double-blind, non-inferiority trial	1:1	357	148 vs. 150	76 centers in 17 countries in Asia, Europe and the United States	CFDC 2 g, q8h	Linezolid 600 mg, q12 h	Meropenem (2 G, Q8h)	7–14	Hospital-acquired, ventilator-associated or health-care-associated pneumonia	*K. pneumoniae, P. aeruginosa, A. baumannii, E. coli, E. cloacae, S. maltophilia*	*F1, F2, F3, F4, F5*
Simon Portsmouth	2018	Phase II, randomized, double-blind, non-inferiority trial	2:1	495	300 vs. 148	67 hospitals in 15 countries	CFDC 2 g, q8h	None	Imipenem/Cilastatin (1 G, Q8h)	7–14	cUTI with or without pyelonephritis or those with acute uncomplicated pyelonephritis	*E. coli, K pneumoniae, P. aeruginosa, Proteus mirabilis, E. cloacae* complex, etc.	*F1, F2, F3, F4*
Eric P. Skaar	2021	Randomized, double-blind, Phase 3	1:1	286	148 vs. 150	76 centers in 17 countries in Asia, Europe and the United States	CFDC 2 g, q8h	Linezolid 600 mg, q12 h	Meropenem (2 G, Q8h)	7–14	Hospital-acquired, ventilator-associated or health-care-associated pneumonia	*K. pneumoniae, P. aeruginosa, A. baumannii, E. coli, E. cloacae, S. maltophilia*	*F1, F2, F3, F5*
Matteo Bassetti	2020	Phase III, randomized, open-label trail	2:1	118	80 vs. 38	95 hospitals 16 countries in South America, North America, Europe and Asia	CFDC 2 g, q8h	None	Meropenem (2 G Q8h)	7–14	Nosocomial pneumonia, bloodstream BSI, cUTI	CRE	*F1, F2, F3, F4, F5*
Shabnam Naseer	2021	Rphase III, randomized, double-blind,	2:1	150	101 vs. 49	Eastern Europe	CFDC 2 g, q8h	-	Imipenem	7–14	Nosocomial pneumonia, bloodstream BSI, cUTI	*A. baumannii, K. pneumoniae, P. aeruginosa, S. maltophilia Gram-negative bacteria*	*F1, F5*
Romaric Larcher	2022	Observational cohort	-	30	24 vs. 6	French	CFDC 2 g, q8h	None	IMI-REL: 0.5 g/0.25 g CAZ-AVI-ATM: 2.5 g/0.5 g/2 g	-	LRTI, IAI, BJI, SSTI, Meningitis, Trauma	Gram-negative bacteria	*F1, F2, F3, F5*
Marco Falcone	2022	Observational cohort	-	124	47 vs. 77	Italy	CFDC 2 g, q8h	Tigecycline - Fosfomycin -	Colistin: 4.5 Million IU/Q 12h, Tigecycline: 100 Mg/Q 12h, Gentamicin: 5 Mg/Kg /Qd, Fosfomycin: 12–24 G/Day, Ampicillin/Sulbactam: 3 G/Q6h, Meropenem: 1-2 G/Q8h	-	BSI, VAP, other	CRAB	*F2, F3, F5*
A. Russo	2023	Observational cohort	-	73	5 vs. 13	Italy	CFDC 2 g, q8h	13	Colistin：9 Million IU/Qd, Tigecycline：200 Mg/Qd, Gentamicin：5 Mg/Kg /Qd, Fosfomycin：12–24 G/Day, Ampicillin/Sulbactam：3g/Q6h, Meropenem：1-2g/Tid	7–14	VAP	CRAB	*F5*
Davide Fiore Bavaro	2023	Observational cohort	-	118	26 vs. 44	Italy	CFDC 2 g, q8h	Tigecycline, Fosfomycin, Ampicillin/Sulbactam	Tigecycline：200 Mg/Qd, Fosfomycin：12–24 G/Day, Ampicillin/Sulbactam：3g/Q6h	-	BSI	CRAB	*F3, F5*
Maria Mazzitelli	2023	Observational cohort	-	111	38 vs. 37	Italy	CFDC 2 g, q8h	Tigecycline, Fosfomycin, Meropenem	Tigecycline：200 Mg/Qd, Fosfomycin：12–24 G/Day, Meropenem：1-2 G/Tid	7–14	BSI, VAP, cUTI, other	CRAB	*F1, F2, F5*
Emanuele Rando	2023	Observational cohort	-	121	42 vs. 51	Italy	CFDC 2 g, q8h	Tigecycline, Gentamicin, Fosfomycin	Tigecycline：200 Mg/Qd, Gentamicin：5 Mg/Kg /Qd, Fosfomycin：12–24 G/Day	-	VAP	CRAB	*F2, F5*

F1: Clinical response; F2: Microbiological response; F3: Adverse events (AEs); F4: Serious adverse events (SAEs); F5: Mortality; CFDC: Cefiderocol; BSI: bloodstream infections; cUTI: complicated urinary tract infections; IAI: intra-abdominal infection; LRTI: low respiratory tract infection; SSTI: skin and soft tissue infection; BJI: bone and joint infection.

included studies. In terms of clinical response, microbiological response, and mortality, subgroup analyses were conducted according to population type (mMITT population: test of cure, TOC; end of treatment, EOT, and follow-up, FUP.), causative pathogens, and infection types.

Results

Literature screening

From the databases (PubMed, n = 854; Embase, n = 1075; Cochrane, n = 39; Web of Science, n = 635), 2603 relevant documents were identified in which 1620 articles were duplicate. After screening the title and abstracts, a total of 983 articles were deemed ineligible and subsequently excluded (330 reviews, 167 conference abstracts, 7 publicity, and educational material, and 41 erratum/editorial). Then, 113 full texts were comprehensively reviewed by two investigators. Finally, 11 studies [12-16,20-25] were included in the analysis. The detailed procedure of the article selection is shown in Figure 1.

Study characteristics

Table 1 provides a summary of the characteristics of the included studies. After a comprehensive selection, 1,673 patients across 11 studies (five RCT and six observational studies) were analyzed. Clinical response was reported in 7 studies (1,358 patients) [12-16,21,23], microbiological response in 8 studies (1,334 patients) [12,13,15,16,20,21,23,24], AEs in 7 studies (1,466 patients) [12,13,15,16,20-22], SAEs in 3 studies (896 patients) [12,13,15], and mortality in 8 studies (980 patients) [13-16,20,21].

CFDC was administrated in the intervention group (Table 1) with a dose of 2 g every 8 hours by intravenous infusion. Three antimicrobial agents were given in the control group, including meropenem, polymyxin, and imipenem-cilastatin. Meropenem was the most common treatment regimen in the control group. The antibiotic dosage was adjusted for patients with kidney injury according to creatinine clearance. The site of infection differed across the studies, primarily involving the urinary tract, HAP, VAP, BSI, and HCAP. In all included studies, all patients were infected with Gram-negative pathogens (eco, kpn, pae, and others).

Quality of the studies

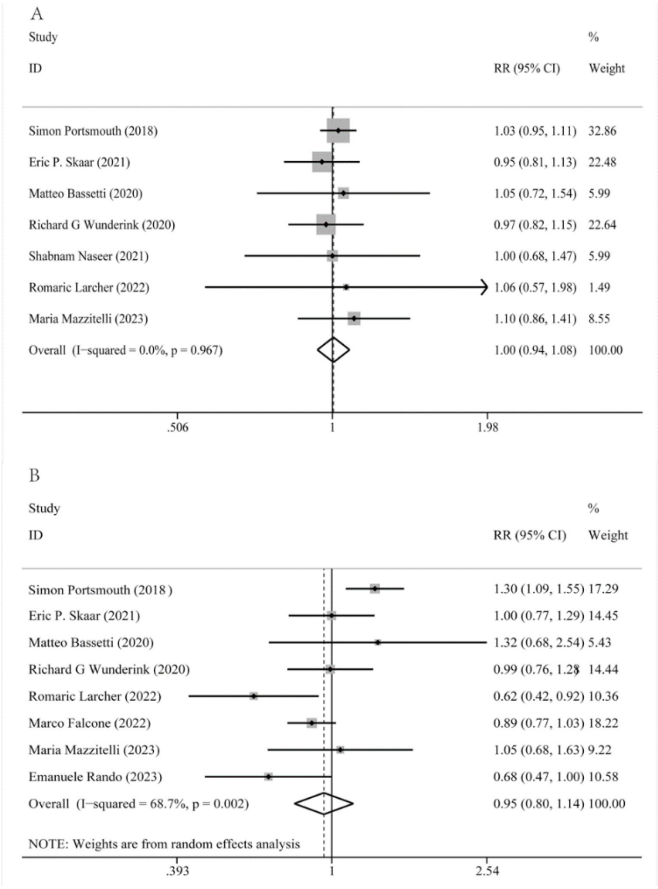
All RCTs demonstrated a low risk of bias and detection bias, in which four studies were double-blind (Supplementary Figure 1). The quality assessment was conducted using the Review Manager. The ROBINS-I tool suggested an overall low to moderate risk of bias with some studies indicated a serious risk (Supplementary Table 2). Therefore, most studies were of relatively high quality.

Outcome measures

Clinical response

Without considering a specific type of infection, seven studies reported the clinical response of CFDC compared to carbapenems/other antibiotics (meropenem, polymyxin, imipenem-cilastatin). The fixed-effects model was adopted for data analysis, and the results showed a comparable effect of CFDC and carbapenems/other antibiotics (RR = 1.00, 95% CI 0.94–1.08, I^2 = 0%), with no significant difference between the two groups (Figure 2A). Our results were similar to the clinical response in the mMITT groups in TOC, EOT, and FUP (Table 2). However, the efficacy of CFDC was not significantly different from the control group, particularly in patients with other types of infections (Table 2).

Figure 2. Forest plots showing RR with 95% CI of efficacy outcomes: **A.** Clinical response; **B.** Microbiological response.



Microbiological response

The microbiological response was reported in eight studies (n = 1,334 patients). The pooled analysis showed that CFDC had similar efficacy in microbial eradication compared to the control drugs (e.g., meropenem, polymyxin, and imipenem-cilastatin) (RR = 0.95 95% CI = 0.80-1.14, $p = 0.596$) (Figure 2B) with significant heterogeneity (I^2 = 68.7%). A pooled analysis demonstrated that patients in the FUP group exhibited a significantly higher response among the mMITT population (RR = 1.25 95% CI = 1.05-1.49, p = 0. 014). According to the subgroup analysis by infection types, CFDC showed more effective than carbapenems in treating cUTI (Table 2).

AEs and SAEs

The analysis demonstrated no differences in AEs and SAEs between the CFDC and control groups. AEs were reported in seven studies (n = 1,446 patients), with a pooled RR of 0.89 (95% CI 0.73-1.07; I^2 = 75.9%). Meanwhile, SAEs were outlined in three studies (n = 896 patients) with a pooled RR of 1.65 (95% CI 0.83-1.32; I^2 = 39.2%) (Figure 3).

Mortality

The mortality rate was reported in six studies involving 980 patients. The results showed that mortality in the CFDC group was similar to the control

Figure 3. Forest plots showing RR with 95% CI of outcomes, including adverse events (AEs) and serious adverse events (SAEs).

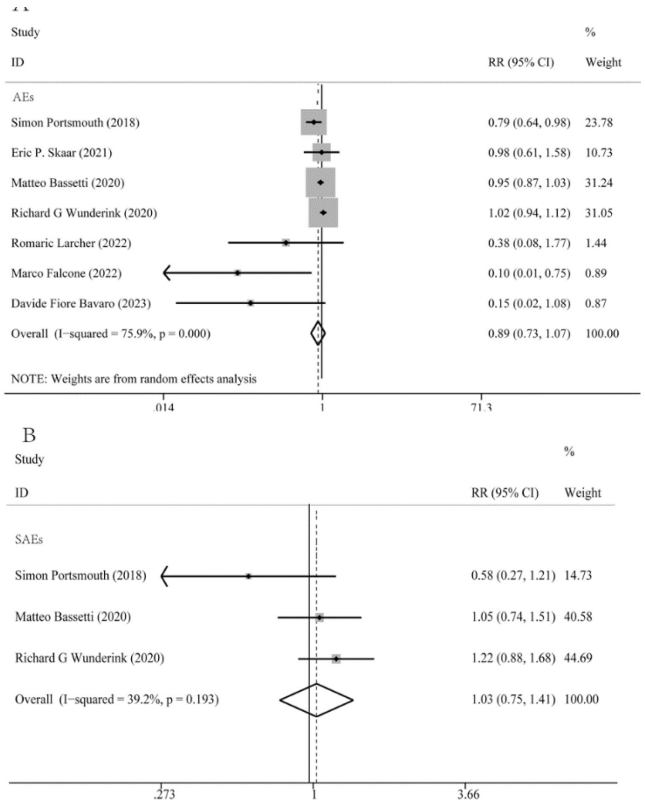


Table 2. Data extraction of included studies in the meta-analysis Subgroup analysis of clinical response, microbiological response and mortality in the cefiderocol group compared with other treatments.

Subgroup	Clinical response			Microbiological response			Mortality		
	RR (95% CI)	No. of participants (no. of studies)	*p*	RR (95% CI)	No. of participants (no. of studies)	*p*	RR (95% CI)	No. of participants (no. of studies)	*p*
EOT	0.98 (0.93, 1.04)	4	0.582	1.05 (0.87, 1.26)	3	0.616	NA	0	NA
TOC	0.99 (0.92, 1.07	5	0.889	0.97 (0.82, 1.15)	6	0.719	NA	0	NA
FUP	1.10 (0.98, 1.22)	3	0.1	1.25 (1.05, 1.49)	3	0.014	NA	0	NA
Infections									
Nosocomial pneumonia	0.98 (0.72, 1.34)	2	0.913	1.00 (0.88, 1.00)	2	0.978	NA	0	NA
BSI	1.10 (0.81, 1.35)	2	0.372	NA	0	NA	NA	0	NA
cUTI	0.94 (0.75, 1.17)	3	0.57	1.32 (1.11, 1.57)	2	0.003	NA	0	NA
Pathogens									
K. pneumoniae	1.13 (0.91, 1.39)	2	0.267	NA	0	NA	0.93 (0.43,2.03)	2	0.974
P. aeruginosa	0.76 (0.43, 1.34)	2	0.347	NA	0	NA	0.43 (0.23,0.95)	2	0.66
A.baumannii	0.94 (0.79, 1.12)	3	0.492	NA	0	NA	0.69 (0.48,0.97)	5	0.035
CRE									
N	1.03 (0.95, 1.11)	1	0.527	1.30 (1.09, 1.55)	1	0.004	NA	0	NA
Y	0.93 (0.90, 1.10)	5	0.885	0.93 (0.84, 1.03)	7	0.186	NA	0	NA
day 14 ACM	NA	0	NA	NA	0	NA	0.95 (0.64,1.41)	6	0.134
day 28 ACM	NA	0	NA	NA	0	NA	0.86 (0.49,1.51)	4	0.599
Age group									
< 65 years	NA	0	NA	NA	0	NA	1.79 (0.95,1.16)	2	0.498
≥ 65 years	NA	0	NA	NA	0	NA	1.92 (0.49,7.49)	2	0.561
APACHE II group									
< 15	NA	0	NA	NA	0	NA	1.26 (0.61,2.58)	2	0.963
≥ 15	NA	0	NA	NA	0	NA	1.92 (0.49,7.49)	2	0.347
Creatinine clearance group									
< 30 (severe)	NA	0	NA	NA	0	NA	1.46 (0.63,3.37)	2	0.936
30 to 50 (moderate)	NA	0	NA	NA	0	NA	0.86 (0.19,3.81)	2	0.134
> 50 to 80 (mild)	NA	0	NA	NA	0	NA	1.61 (0.64,4.06)	2	0.709
> 80 to < 120 (normal)	NA	0	NA	NA	0	NA	1.64 (0.51,5.26)	2	0.722
> 80 to < 120 (normal)	NA	0	NA	NA	0	NA	0.76 (0.27,2.12)	2	0.795

TOC: test of cure; EOT: end of treatment; FUP: follow-up; ACM: all-cause mortality; BSI: bloodstream infections; cUTI: complicated urinary tract infections; APACHE II: Acute Physiology and Chronic Health Evaluation II; CRE: carbapenem-resistant *Enterobacteriaceae.*

group (RR = 0.74 95% CI 0.54-1.00; I^2 = 68.4%) (Figure 4). Particularly, CFDC showed a reduced mortality compared to the controls for infections caused by *A. baumannii* (RR = 0.69, 95% CI 0.48–0.93; I^2 = 57.3 %).

Sensitivity analyses

A sensitivity analysis was conducted to determine the effect of each study and the results were unaffected after the exclusion of each study. Furthermore, the results for clinical response, microbiological response, AEs and SAEs, and mortality were similar (Supplementary Figure 2) after the exclusion of each study.

Publication bias

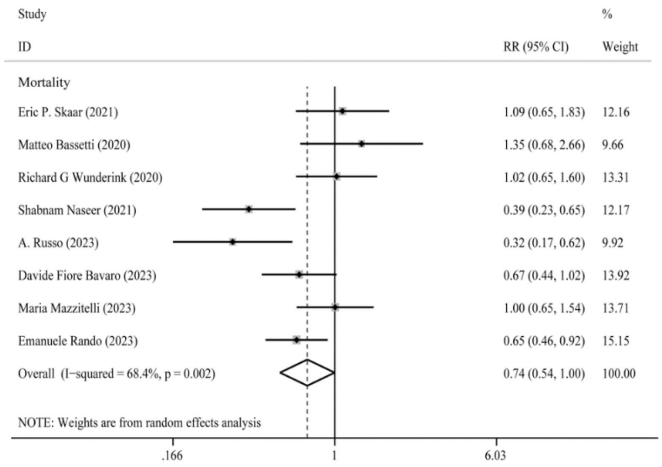
The results of Egger's test indicated no publication bias for clinical response (PEgger = 0.947), microbial eradication (PEgger = 0.996), SAEs (PEgger = 0.321), and mortality (PEgger = 0.089) (Supplementary Figure 3), except for publication (PEgger = 0.026).

Discussion

Eleven studies were analyzed and showed that CFDC was comparable to the standard treatment against GNB infections. Thus, it could potentially serve as an alternative option for addressing anti-infective treatments. CFDC is similar to carbapenems in terms of safety, [26,27]. GNB can cause various complex infections, including cUTI, pneumonia, and BSI [28,29]. In particular, CFDC is significantly more effective than imipenem/cilastatin in combating infections caused by cUTI [28,29]. The extensive use of carbapenems contributes to the increase in GNB resistance [30,31]. CRE, as one of the multidrug-resistant GNBs, poses a significant global health threat due to its adverse clinical outcomes with 40% - 50% mortality rate [32,33]. Drug-resistant genes have been found in some strains, such as cloned ST11-KL64 strains resistant to colistin and tigecycline [34-36]. Therefore, it is crucial to identify and develop alternative treatments that are both more effective and safer.

To addressing this threat, CFDC has been developed as a novel iron carrier cephalosporin to complement or substitute current antimicrobial agents. It is transported by the iron transport protein, which penetrates the extracellular membrane of Gram-negative rods to the human body [37,38]. CFDC exhibits good antibacterial activity in vitro against CRE, CRAB, and multidrug-resistant *Pseudomonas aeruginosa* by acting on penicillin-binding protein 3 (PBP3) [39].

Figure 4. Forest plots showing RR with 95% CI of outcomes: mortality.



In the present meta-analysis, CFDC exhibited comparable efficacy to carbapenems in treating Gram-negative infections, which is consistent with previous studies [40,41]. Regarding microbiological responses, the CDFL group achieved similar clinical cure rates, particularly against the subgroups of nosocomial pneumonia and BSI, to the control group except for cUTI. Furthermore, the microbial eradication rate of non-CRE strains was higher than CRE strains. The microbial eradication rate of the two regimens did not have a statistically significant difference in the other subgroups ($p > 0.05$). Meanwhile, CFDC is time-dependent and largely excreted in urinary, approximately 90.6% of the administered dose [42]. CFDC was superior to carbapenems in eradicating bacteria in cUTI. Notably, in addition to the good pharmacokinetic-pharmacodynamic properties of CFDC in treating urinary tract infections, CFDC for the treatment of lung infections caused by carbapenem-resistant *P. aeruginosa, A. baumannii,* and *K. pneumoniae* strains. CFDC significantly reduced clinical isolates of CRAB, CRKP, and CRPA, at a 2g, q8h (3h intravenous drip) dosage, in immunocompetent-rat respiratory tract infection model [43]. Furthermore, it was also effective against multidrug-resistant bacteria, such as class B metallo-β-lactamases (e.g., NDM, IMP, and VIM), extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* carbapenemases (KPCs), and class D β-lactamases (e.g., OXA type), *Pseudomonas aeruginosa*, A*cinetobacter baumannii*, and *Stenotrophomonas maltophilia* [44,45]. Studies have shown that CFDC remains active against GNB. It is effective even against

ceftazidime/avibactam, ceflozar/tazobactam, and colistin-resistant strains [46]. Therefore, CFDC can potentially serve as a viable treatment for GNB infections, particularly carbapenems.

In this study, a similar incidence of AEs, SAEs, and mortality was noticed in the CFDC-treated group compared with the control treatment group, the high-dose meropenem prolonged titration group, and the imipenem/cilastatin treatment group [12,13,15]. During the phase III clinical trials, both CREDIBLE-CR and APEKS-NP studies reported several adverse events, including diarrhea (19% vs. 8.8%), elevated alanine aminotransferase (7% vs. 6.1%), elevated aspartate aminotransferase (8% vs. 6.8%), pneumonia (7% vs. 7.4%), anemia (8% vs. 8.1%) and pleural effusion (8% vs. 6.8%) [44,46]. In addition, several serious adverse events (≥ 8%) induced by CREDIBLE-CR treatment were fever (14%), infectious shock (13%), vomiting (13%), pressure ulcers (10%), constipation (9%) and hypotension (8%) [44]; in the phase III APEKS-NP trial, serious adverse events (≥ 6% probability) were also induced by cUTI (15.5%) and hypokalemia (10.8%). CFDC was well-tolerated in both Phase II and Phase III studies. Although the mortality rate of CFDC in the treatment of ventilator-associated pneumonia (VAP) was lower in the CRAB than in the control group [24], the ability of this study to further evaluate these trends is limited due to the small sample size, heterogeneity/reporting of studies, and cases of infection caused by multiple pathogens. However, no significant differences in pathogen-specific results were found in our study.

To minimize the potential for bias, both observational studies and RCTs were screened with stringent inclusion and exclusion criteria. Overall, the risk of bias was found to be low. In terms of clinical response, microbiological response, and mortality, subgroup analyses were conducted according to population types, causative organisms, and types of infection.

However, this review has some limitations that need to be considered. First, the CFDC group differed in dose (including co-medication) and duration of treatment, which may affect the results. The heterogeneity in comparator groups in terms of the antibiotic agents should be taken into account in the analysis. Second, a limited number of studies, including RCTs, had been included. Finally, limitations of our meta-analysis include the lack of prospective studies is a potential limitation of any systematic review.

Conclusions

This meta-analysis showed that CFDC and standard therapy had comparable efficacy in treating GNB infections. In particular, CFDC exhibited good microbiological clearance in cUTI. However, further investigations are required, both in vitro and in vivo, to explore more about the synergistic antibacterial effect of CFDC combined with other antibacterial drugs. With these promising attributes, CFDC can potentially become a new class of antimicrobials for treating GNB infections.

Availability of data and materials

The original contributions presented in the study are included in the article/Supplementary material. Further inquiries can be directed to the corresponding author.

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Authors' Contributions

Conceptualization: Lin Su, Xiaocui Huang, Data curation: Yiduo Zhang. Formal analysis: Wenjie Zhou. Funding acquisition: Fan Yu and Xiaocui Huang. Project administration: Fan Yu. Writing - original draft: Lin Su, Xiaocui Huang. Writing - review & editing: Chao Li, Fan Yu

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Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

Supplementary Table 1. Search strategy.

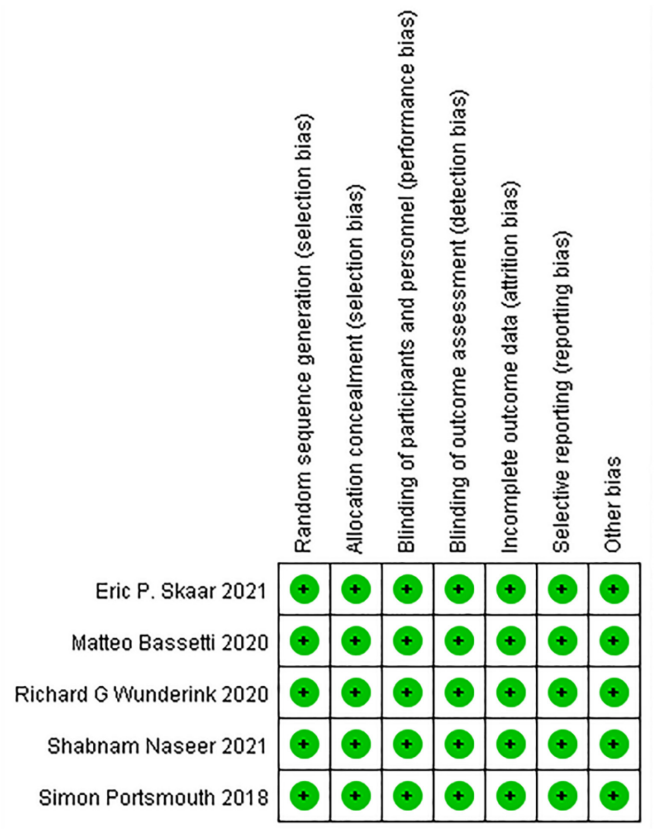
Database	No.	Expressions	Result
PubMed	#1	("cefiderocol" [Supplementary Concept]) OR ((cefiderocol[Title/Abstract])OR(S-649266[Title/Abstract]))	854
Embase	#1	'cefiderocol'/exp	1075
	#2	'cefiderocol':ab,ti	
	#3	's 649266':ab,ti	
	#4	(#1 or #2 or #3)	
Cochrane Library	#1	(cefiderocol):ti,ab,kw OR S-649266):ti,ab,kw	39
Web of science	#1	TS=(cefiderocol) OR TS=(S-649266)	635

P: People with gram-negative bacteria infection; E: Cefiderocol monotherapy as a definitive antibiotic agent; C: Anti-gram-negative bacteria monotherapy, which including imipenem, Meropenem; O: 30-day all-cause mortality measured from infection diagnosis; S: Comparative studies, with no other defined restrictions. This would include RCT and prospective/retrospective observational studies, so long as cefiderocol is compared to one or more anti-gram-negative bacteria carbapenems; Question: Outcomes of cefiderocol for treatment of gram-negative bacteria infection: A Systematic Review and Meta-Analysis.

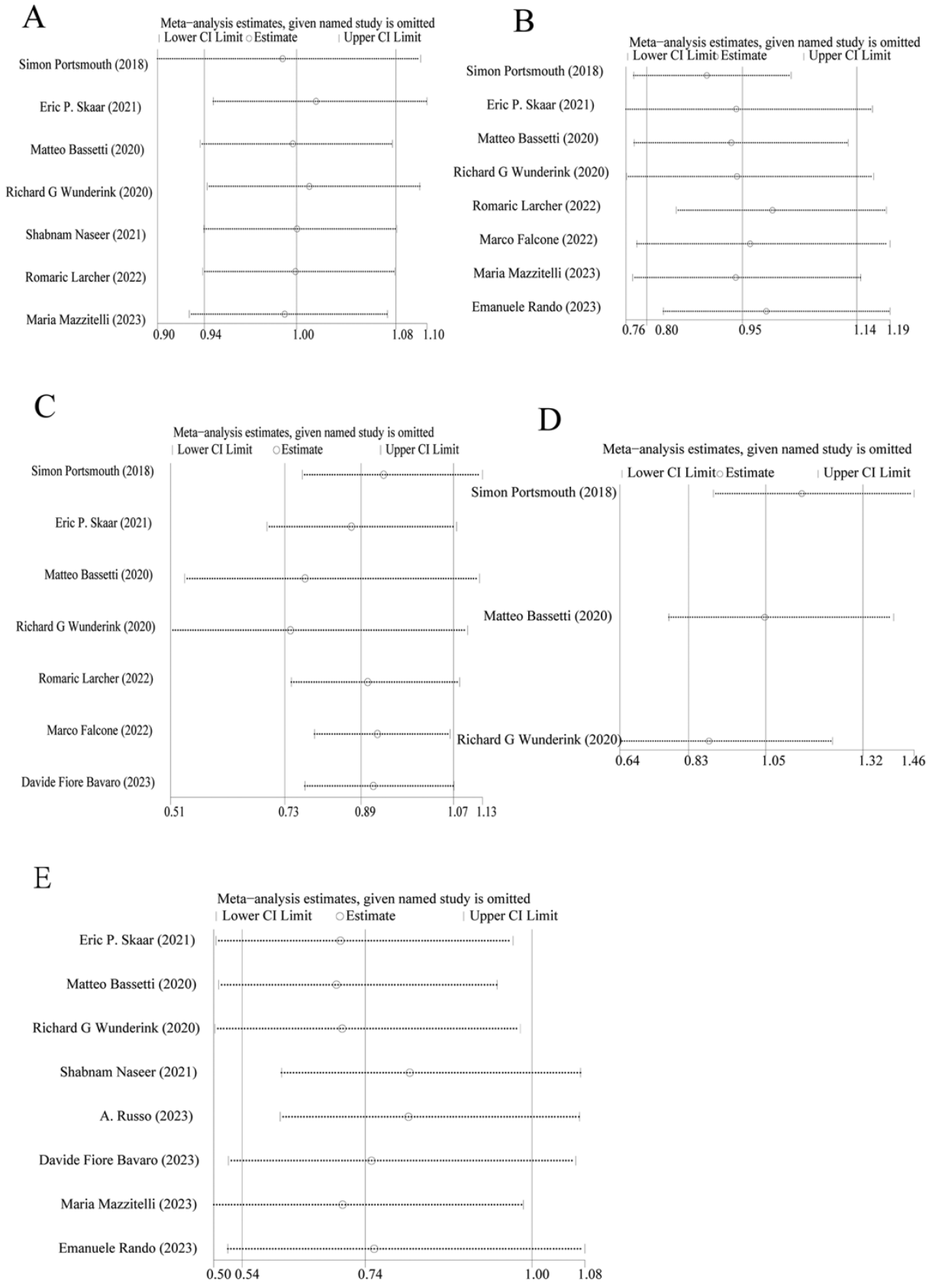
Supplementary Table 2. ROBINS-I tool of the observational studies.

Study	Confounding	Selection bias	Bias in measurement classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Larcher R	L	M	L	L	L	L	L
Falcone M	L	M	L	L	L	L	L
Russo A	L	M	L	L	L	L	L
Bavaro DF	L	M	L	L	L	L	L
Mazzitelli M	L	M	L	L	L	L	L
Rando E	L	M	L	L	L	L	L

Supplementary Figure 1. summary of risk of bias analysis for the RCTs studies.



Supplementary Figure 2. Sensitivity analyses of the outcomes. **A.** Clinical response; **B.** Microbiological response; **C.** Adverse events (AEs); **D.** Serious adverse events (SAEs); **E.** Mortality.



Supplementary Figure 3. Egger's test of the outcomes. **A.** Clinical response; **B.** Microbiological response; **C.** Adverse events (AEs); **D.** Serious adverse events (SAEs); **E.** Mortality.