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Comparative efficacy and safety of antipseudomonal β-lactams for pediatric febrile neutropenia

A systematic review and Bayesian network meta-analysis

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Abstract

Background: Antipseudomonal β-lactams have been used for the treatment of febrile neutropenia (FN); however, the efficacy and safety of antipseudomonal β-lactams in pediatric patients remain unclear. The aim of this study was to comprehensively compare the efficacy and side effects of optional antipseudomonal β-lactams for pediatric FN.

Methods: PubMed, Embase, Medline, and Cochrane Library were systematically searched from their inception to December 18, 2020. Eligible randomized controlled trials in which pediatric FN patients were treated with an empiric monotherapy of antipseudomonal β-lactams were selected. Data synthesis was performed using WinBUGS 14.0 software and meta packages implemented in R 3.6.2. Random-effects network meta-analysis was performed, and dichotomous data were pooled as odds ratios with 95% confidence intervals. The primary outcome was treatment success without modification; the secondary outcomes were adverse events (AEs), all-cause mortality, and new infections. The GRADE tool was used to assess the quality of the evidence. The protocol was registered with PROSPERO ID CRD42021226763.

Results: Eighteen studies with 2517 patients were included. The results showed no statistically significant difference between the optional antipseudomonal β-lactams in the outcomes of treatment success without modification, all AEs, all-cause mortality, and new infections for pediatric FN. Based on the results of Bayesian rank probability, meropenem was ranked highest among all the treatment options with regard to treatment success without modification benefit; ceftazidime and meropenem were associated with a lower risk of AEs; cefoperazone/sulbactam and piperacillin/tazobactam were associated with a lower risk of mortality, and piperacillin/tazobactam and meropenem were associated with a lower risk of new infections. The quality of evidence was moderate.

Conclusions: Meropenem and piperacillin/tazobactam were found to be better with regard to treatment success without modification, with a comparable safety profile. Therefore, our findings support the use of meropenem and piperacillin/tazobactam as a treatment option for pediatric FN patients.

Abbreviations: AEs = adverse events, CI = confidence interval, FN = febrile neutropenia, OR = odds ratio, RCT = randomized controlled trial, SUCRA = surface under the cumulative ranking curve.

Keywords: antipseudomonal β-lactams, febrile neutropenia, network meta-analysis, pediatric, systematic review

1. Introduction

Febrile neutropenia (FN) is a common complication of cancer chemotherapy, and is related to significant morbidity and mortality in pediatric patients.[1] Over the last 50 years, antipseudomonal β-lactams have played an important role in empirical monotherapy for high-risk FN patients.[2–6] Many clinical trials have been performed to evaluate the efficacy and safety of various antibiotic therapies for FN in adults. These trials

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have led to the development and publication of clinical guidelines for the management of adult FN[2,7]; however, such guidelines are lacking for pediatric patients.[8]

Empirical common antibiotic monotherapy is required to provide a broad antibacterial spectrum, including for *Pseudomonas aeruginosa*. Therefore, antipseudomonal β-lactams are generally the choice of empiric therapies for high-risk FN patients. Guidelines recommend 5 first-line antipseudomonal β-lactams, including cefepime, meropenem, imipenem/cilastatin, piperacillin/tazobactam, and ceftazidime.[9,10] Among these antipseudomonal β-lactams, cefepime, piperacillin/tazobactam, and carbapenems with a broad spectrum exhibit antibacterial activity against methicillin-susceptible *Staphylococcus aureus*, *Streptococcus viridans*, and *Streptococcus pneumoniae*.[11,12] Cefepime and piperacillin/tazobactam offer better coverage of the antibacterial spectrum against extended spectrum β-lactamases (ESBLs)[13,14]; therefore, carbapenems are the treatment of choice against ESBL-producing gram-negative bacteria.[15] In addition to these first-line antibiotics, many other antipseudomonal β-lactams, such as cefoperazone/sulbactam and cefozopran, have been included in published randomized controlled trials (RCTs). However, physicians lack clinical evidence on the better choice among the recommended β-lactams for patients with FN, especially for pediatric patients.

Previous studies have assessed the efficacy and safety of empirical antibiotic therapy for FN.[4,16–19] However, most of these studies included all the ages groups of FN patients. Only 1 pairwise meta-analysis evaluated carbapenems in comparison with antipseudomonal penicillin for the treatment of pediatric FN.[19] However, most of these studies evaluated only direct comparisons, and the efficacy and safety of common antipseudomonal β-lactams remain inconclusive. In a complex setting of different treatment choices, including several optional interventions and some therapeutic strategies that have not been directly compared, a network meta-analysis can provide direct and indirect comparisons of various treatment strategies simultaneously within a single network and rank the optional treatments according to comparative efficacy and safety.[20] Therefore, we conducted a systematic review and network meta-analysis to comprehensively compare the efficacy and safety of optional antipseudomonal β-lactams for the treatment of pediatric FN patients. We evaluated treatment success without antibiotic modification as the primary outcome. The occurrence of adverse events (AEs), all-cause mortality, and new infections were also assessed as secondary outcomes.

2. Methods

2.1. Study design

The study was approved by the ethics institutional review board of the People's Hospital of Guangxi Zhuang Autonomous Region. A systematic review and network meta-analysis was conducted following the protocol registered with PROSPERO (number CRD42021226763). This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement extension for network meta-analysis.[21]

2.2. Search strategy

PubMed, Medline (via OVID SP), Embase (via OVID SP), and Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched, with dates of search ranging from the time of their inception to December 18, 2020. The search formulae are presented in the Item S1, Supplemental Digital Content, http://links.lww.com/MD2/A596 (which illustrates the specific search strategies). The search was carried out without the limitation of publication year. No language restrictions were imposed. To identify additional articles missed by using the above-mentioned search strategy, we also scanned the reference lists of all included trials and relevant reviews.

2.3. Inclusion criteria

Studies that fulfilled the following criteria were included: participants: We included pediatric FN patients who received chemotherapy for solid tumors or hematological malignancies. Febrile episodes were classified according to the kind of infection as microbiologically defined infection, clinically defined infection, and fever of unknown origin; interventions and comparisons: Pediatric FN patients in both interventions empirical monotherapy with antipseudomonal β-lactams; outcome: The primary outcome was treatment success without modification; we defined treatment success without modification as the outcome that satisfies one of the traditional definitions of treatment success, and we did not include success with modification as an outcome in this study. The secondary outcomes were any AE, which include incidence of any AE, discontinuation of treatment due to AEs, and specific AEs; all-cause mortality, all-cause mortality at the end of study follow-up; new infections, new, persistent, or worsening symptoms and/or signs of infection associated with the isolation of a new pathogen or the development of a new site of infection; study design: RCT.

2.4. Exclusion criteria

We did not include trials on adult patients with FN. Simultaneous administration of granulocyte colony-stimulating factor was accepted, but granulocyte transfusion was excluded. Adding the same anti-methicillin-resistant Staphylococcus aureus drug or aminoglycoside for both arms was accepted; adding quinolone for both the interventions was also not accepted; the trials that were not RCTs, such as case reports, meeting abstracts, and observational studies and reviews without usable data, and meta-analyses were excluded; studies without the primary or secondary outcomes and those with unavailable full-text article or unextractable data were excluded.

2.5. Data collection and quality assessment

Two reviewers (Li and Xi) independently extracted the data, including the information according to the study characteristics, such as country, age, sex, and sample size. The intervention protocol of different antipseudomonal β-lactams, such as the dosage, frequency, and course; primary and secondary outcome data; and the definition of FN and primary outcome were also collected. A third reviewer (Liang) examined the consistency of the extracted data.

The methodological quality of the included studies was evaluated by Li and Xi, based on the Cochrane risk-of-bias tool.[22] Methodologists were consulted when they came across discrepancies. In terms of the assessment criteria, the domain of the risk-of-bias tool of each individual included study was graded as one of the following 3 levels of risk of bias: high, unclear, or low risk of bias with justifications.

2.6. Data synthesis and analysis

Pairwise meta-analysis was performed using the DerSimonian and Laird random-effects model[23] by "meta" (version 4.9-4)[24] package implemented in R software version 3.6.2 (R Foundation for Statistical Computing). For dichotomous outcomes, the pooled results were expressed as odds ratios (ORs) with 95% confidence interval (95% CI). If 95% CI of OR did not include 1, the difference between the comparisons was considered statistically significant. The heterogeneity of treatment estimates among the studies in each pairwise meta-analysis was examined using χ^2 tests and the corresponding I^2 statistics.[25] In consideration of the heterogeneity between the included trials, we performed a random-effects network meta-analysis to combine the direct and indirect evidence of all the treatment effects using WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) software based on the Bayesian hierarchical model and Markov Chain Monte Carlo algorithm. In the WinBUGS program, the number of iterations was set to 100,000, and the first 10,000 iterations were regarded as burn-in for annealing to eliminate the impact of the initial value.[26] We ranked antipseudomonal β-lactams for each outcome by the surface under the cumulative ranking curve (SUCRA) probabilities and the posterior probabilities; SUCRA values of 100% and 0% were ranked as the best and worst treatments, respectively, and higher posterior probabilities in each simulation indicated a higher chance of being the best treatment agent.[27]

We performed a loop-specific method to systematically evaluate the inconsistency within every closed triangular or quadratic loop between the direct and indirect sources of evidence.[28,29] We then considered the source of inconsistency to analyze if there is a significant difference between direct and indirect assessment for a specific intervention comparison in the loop.[28] The node splitting approach was used to evaluate inconsistency within the network by separating the comparisons of the direct and indirect evidence.[30] When there were 10 or more trials, we evaluated small-study effects by using a comparison-adjusted funnel plot of treatments to detect the presence of any publication bias in the network meta-analysis.[27,31] Subgroup analyses for the primary outcome were performed based on the following subgroups: pediatric patients with microbiologically defined infection, microbiologically not confirmed but clinically defined infection, and fever of unknown origin.[32,33]

3. Results

3.1. Study identification and selection

In total, 585 records were obtained through a literature search, and 267 duplicate papers were excluded. A total of 318 studies were retained for further analysis. After the evaluation of the titles and abstracts, 256 irrelevant articles were excluded. After reading the remaining 62 full-text papers, 44 studies were excluded for the following reasons: studies with an irrelevant study design (n=40), non-RCTs (n=2), and reviews and meta-analyses (n=2). Finally, 18 studies were included in the meta-analysis. The study selection process was performed according to the PRISMA guidelines, and Figure 1 shows the PRISMA.

3.2. Characteristics of included studies

The main characteristics of the included studies are summarized in Table 1. Overall, 18 trials[34–51] with a total of 2517 pediatric FN patients were included in the present network meta-analysis, and these studies were published from 2001 to 2020. The sample size of the participants in these studies ranged from 40 to 393. All of the included studies adopted the 2-arm trial design, and among the 36 arms in 18 trials, piperacillin/tazobactam, cefepime, meropenem, ceftazidime, cefoperazone/sulbactam, cefozopran, and imipenem/cilastatin were evaluated in 10, 10, 6, 5, 2, 2, and 1 arm, respectively. The definitions of FN and the durations of trials for outcomes are described in Tables S1 and S2, Supplemental Digital Content, http://links.lww.com/MD2/A597, http://links.lww.com/MD2/A598 (which illustrate the definition of the FN and primary outcome).

3.3. Risk of bias assessment

The risk of bias and methodological quality of all the included trials were assessed and are summarized in Figure 2. The random sequence generation of 4 studies[41,42,45,48] used a random number table. The allocation concealment of 3 studies[39,43,48] used the envelope method. Two studies[38,48] adopted a double-blinded design, one of the studies[44] adopted a single-blinded design, and 7 studies[34,35,37,39,40,45,46] adopted an open-label design. All the trials had complete follow-up.

3.4. Overview

The findings of the primary outcomes of network meta-analysis are described in Table 2, and those of the other outcomes are shown in Tables S3 to S5, Supplemental Digital Content, http://links.lww.com/MD2/A599, http://links.lww.com/MD2/A600, http://links.lww.com/MD2/A601 (which illustrate the results of new infections, AEs, and mortality). The results of the traditional meta-analysis and GRADE assessments for outcomes are provided in Table S6, Supplemental Digital Content, http://links.lww.com/MD2/A602 (which illustrates the quality of evidence for the direct comparisons by GRADE). Similar ORs and 95% CIs overlapping in magnitude were observed between network meta-analysis and traditional pairwise meta-analysis. Treatment network plots for the primary outcome and the secondary outcomes are shown in Figure 3 and Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A593 (which illustrates the network plot for secondary outcomes). Rankograms and SUCRA plots of the primary outcome are shown in Figure 4, plots of secondary outcomes are shown in Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A594 (which illustrates the rank probability and SUCRA plots of secondary outcomes), and multidimensional cluster analysis based on SUCRA plots is shown in Figure 5. The results of inconsistency between direct and indirect treatment effects are shown in Table S7, Supplemental Digital Content, http://links.lww.com/MD2/A603 (which illustrates the consistency for each binary outcome network), and testing did not reveal evidence of inconsistency, although the CIs were frequently wide.

3.5. Treatment success without modification

Treatment success without antibiotic modification was reported in 18 studies covering 2438 pediatric patients, of whom 1603 achieved treatment success. The network plots are shown in Figure 3. No antipseudomonal β-lactam treatment significantly increased the treatment success rate without modification for pediatric FN patients (Table 2). Meropenem had the highest rank probability of treatment success rate among all the antipseudo-

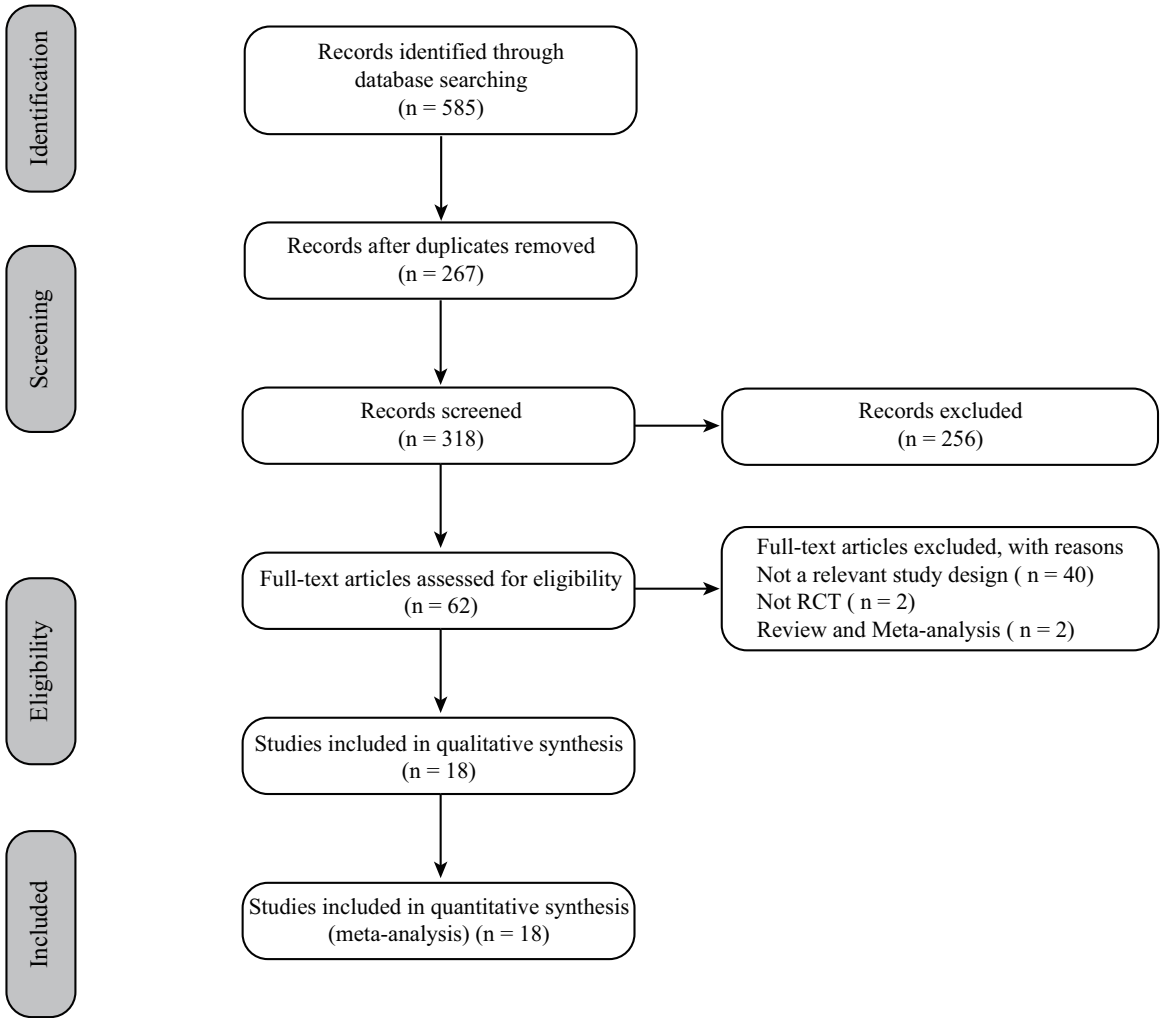

Figure 1. Identification process for eligible RCTs. RCT = randomized controlled trial.

monal β-lactams. The rank probability of treatments based on SUCRAs is shown in the Figure 5.

In the subgroup analysis of microbiologically defined infection, clinically defined infection, and fever of unknown origin pediatric patients, the results did not reveal any difference between the optional antipseudomonal β-lactams (see Tables S8–S10, Supplemental Digital Content, http://links.lww.com/MD2/A604, http://links.lww.com/MD2/A605, http://links.lww.com/MD2/A606, which illustrate the results of treatment success of microbiologically defined infection, clinically defined infection, and fever of unknown origin pediatric patients).

3.6. Any adverse events

Six studies[34,38–40,43,45] that included 1045 patients, observed the occurrence of AEs (see Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A593, which illustrates the network plot for secondary outcomes). No significant difference was found among the antipseudomonal β-lactams. The risk of any AEs was lower in pediatric patients treated with ceftazidime and meropenem than with other optional treatments, based on the rank probability of Bayesian network meta-analysis (see Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A594, which illustrates the rank probability and SUCRA plots of secondary outcomes and Figure 5).

3.7. All-cause mortality

The network meta-analysis of 6 studies[34,35,37,39,40,47] involving 926 patients reporting all-cause mortality was included in the analysis (see Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A593, which illustrates the network plot for secondary outcomes). This analysis revealed no significant difference among the antipseudomonal β-lactams. Cefoperazone/sulbactam and piperacillin/tazobactam ranked higher than other drugs, as it was associated with a lower risk of mortality (see Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A594, which illustrates the rank probability and SUCRA plots of secondary outcomes and Figure 5).

3.8. New infections

Six studies[35,38,43,45,47,48] involving 1041 patients were evaluated for new infections (see Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A593, which illustrates the network plot for secondary outcomes). No statistically significant

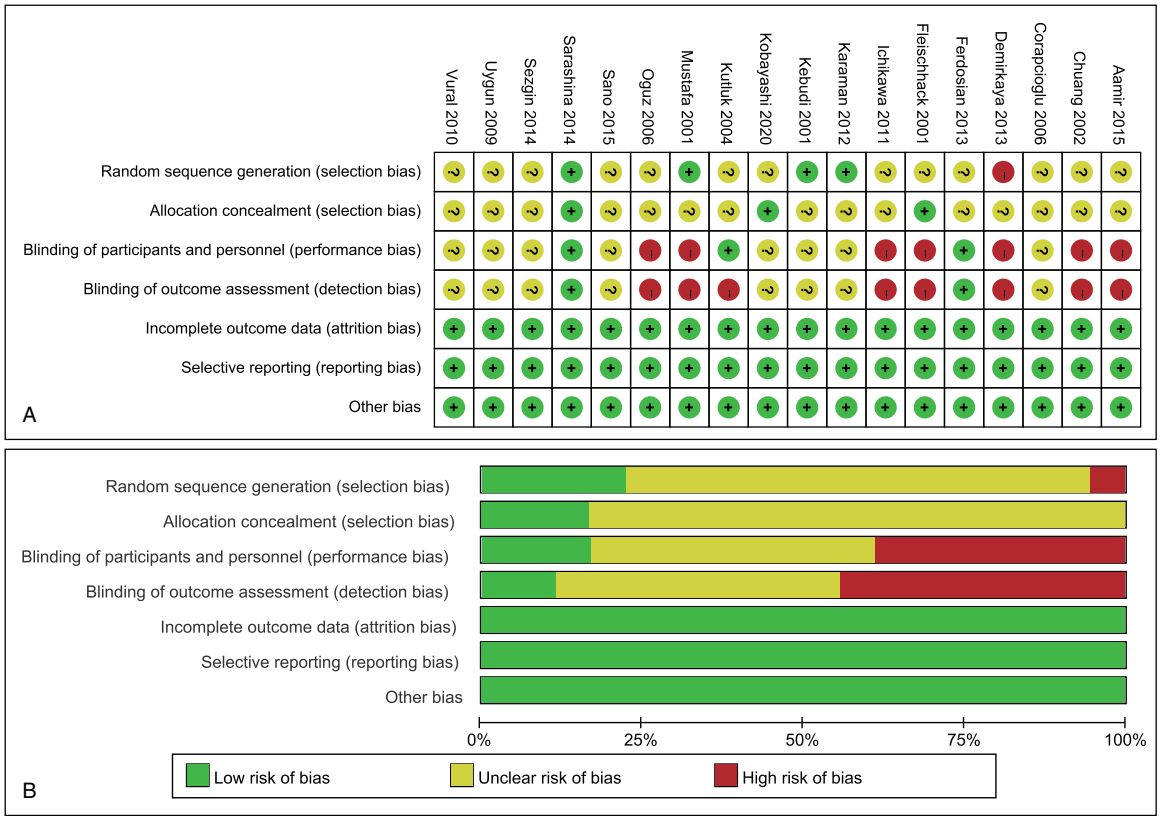

Figure 2. Risk of bias of included studies. (A) Risk of bias summary: judgments about each bias item for each study; (B) Risk of bias summary graph.

difference was noted between the treatment options. Piperacillin/tazobactam and meropenem ranked higher than other drugs, as they were associated with a lower risk of new infections (see Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A594, which illustrates the rank probability and SUCRA plots of secondary outcomes and Figure 4).

3.9. Multidimensional cluster analysis

Multidimensional cluster analysis based on SUCRA was conducted to evaluate the rank probability of antipseudomonal β-lactams for the reported primary and secondary outcomes (Fig. 5). In terms of treatment success without modification, AEs, and new infections, meropenem was superior to the other

Table 1

Characteristics of included studies.

		Pediatric febrile neutropenia			Treatment		
Study	Country	Mean or median age	Sample size (M/F)	Arms	Arm 1	Arm 2	Add on treatment
Aamir 2015	India	6	40 (26/14)	20/20	CFPM (50 mg/kg × 3)	P/T (100 mg/kg × 3)	
Chuang 2002	China	5.6	116 (73/43)	58/58	CFPM (50 mg/kg × 2)	CAZ (50 mg/kg × 3)	
Corapcioglu 2006	Turkey	8.4	50	25/25	CFPM (50 mg/kg × 3)	P/T (90 mg/kg × 4)	
Demirkaya 2013	Turkey	6.3	116 (71/45)	57/59	C/S (33.3 mg/kg × 3)	P/T (90 mg/kg × 4)	AMK (15 mg/kg)
Ferdosian 2013	Iran	5.9	48 (31/17)	26/22	CAZ (50 mg/kg × 3)	MEPM (20 mg/kg × 3)	
Fleischhack 2001	Germany	7.4	342 (174/168)	172/170	CAZ (33.3 mg/kg × 3)	MEPM (20 mg/kg × 3)	
Ichikawa 2011	Japan	8.2	119 (69/50)	62/57	CZOP (25 mg/kg × 4)	P/T (125 mg/kg × 3)	
Karaman 2012	Turkey	4	102 (55/47)	50/52	C/S (33 mg/kg × 3)	P/T (120 mg/kg × 3)	
Kebudi 2001	Turkey	7	63	32/31	CFPM (50 mg/kg × 3)	CAZ (33.3 mg/kg × 3)	
Kobayashi 2020	Japan	9.9	393 (249/144)	193/200	P/T (120 mg/kg × 3)	MEPM (40 mg/kg × 3)	
Kutluk 2004	Turkey	7.4	49	25/24	CFPM (50 mg/kg × 3)	MEPM (20 mg/kg × 3)	
Mustafa 2001	USA	6	104 (63/41)	49/55	CFPM (50 mg/kg × 3)	CAZ (50 mg/kg × 3)	
Oguz 2006	Turkey	8	65 (44/21)	32/33	CFPM (20 mg/kg × 3)	MEPM (50 mg/kg × 3)	
Sano 2015	Japan	5	213 (112/101)	103/110	P/T (112.5 mg/kg × 3)	CFPM (25 mg/kg × 4)	
Sarashina 2014	Japan	6	223 (110/113)	111/112	CZOP (25 mg/kg × 4)	CFPM (25 mg/kg × 4)	
Sezgin 2014	Turkey	5	284 (176/108)	86/198	P/T (120 mg/kg × 3)	MEPM (20 mg/kg × 3)	
Uygun 2009	Turkey	4	127 (64/63)	65/62	P/T (90 mg/kg × 4)	CFPM (50 mg/kg × 3)	
Vural 2010	Turkey	5	63 (41/22)	30/33	I/C (15 mg/kg × 4)	P/T (90 mg/kg × 4)	

AMK = amikacin, C/S = cefoperazone/sulbactam, CAZ = ceftazidime, CFPM = cefepime, CZOP = cefozopran, I/C = imipenem/cilastatin, MEPM = meropenem, P/T = piperacillin/tazobactam.

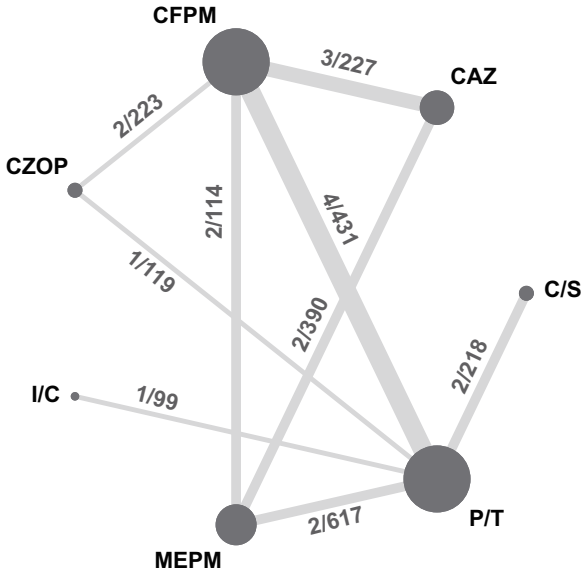

Figure 3. Network plot for treatment success. C/S = cefoperazone/sulbactam, CAZ = ceftazidime, CFPM = cefepime, CZOP = cefozopran, I/C = imipenem/cilastatin, MEPM = meropenem, P/T = piperacillin/tazobactam.

regimens, followed by piperacillin/tazobactam. In addition, piperacillin/tazobactam was dominant in the comprehensive ranking of all-cause mortality.

3.10. Publication bias analysis

This study performed a comparison-correction funnel plot for the primary outcomes to identify publication bias (see Figure S3, Supplemental Digital Content, http://links.lww.com/MD2/A595, which illustrates the funnel plots of primary outcome). When the points distributed in the funnel plot are symmetrical, it suggests that there is no publication bias.[52] The points of the funnel plot showed no sign of asymmetry on either side of the centerline, but there was an angle between the centerline and the correction guideline. This reveals that the results of our study may have some potential publication bias.

3.11. Quality of evidence

We used the GRADE to further assess the quality of evidence for direct evidence. The GRADE assessments for all the outcomes are presented in Table S6, Supplemental Digital Content, http://links.lww.com/MD2/A602 (which illustrates the quality of evidence for the direct comparisons by GRADE). The quality of a majority of direct comparisons of treatment success without modification and AEs was moderate; however, most of the comparisons of all-cause mortality and new infections were of relatively low quality.

4. Discussion

This is the first systematic review and network meta-analysis comparing the efficacy and safety of current optional antipseudomonal β-lactam treatments for pediatric FN patients and assessing multiple outcomes. Several key findings were obtained in this analysis. First, regarding the results of treatment success without modification, although no antipseudomonal β-lactams option was significant among the comparisons, meropenem was ranked highest among all the treatment options. Second, ceftazidime and meropenem were associated with a lower risk of AEs; however, no significant differences were found among the treatment options. Third, cefoperazone/sulbactam and piperacillin/tazobactam were associated with a lower risk of mortality, although there was no significant difference among the compared treatments. Finally, piperacillin/tazobactam and meropenem were associated with a lower risk of new infections without significant difference among the compared treatments. These findings indicate that no significant difference was found in the efficacy and safety outcomes of the evaluated antipseudomonal β-lactams in pediatric FN patients.

A previous meta-analysis[4] evaluated antipseudomonal β-lactams for adult and pediatric FN patients, and showed that imipenem/cilastatin, piperacillin/tazobactam, and meropenem could be used as the first-line empirical antibiotic monotherapy for FN. However, most of the included patients were adults. Similar to the previous meta-analyses, our study indicated that meropenem and piperacillin/tazobactam were associated with a higher rank of clinical efficiency and safety profile for the treatment of pediatric FN patients, although no significant difference was found in the comparison of outcomes. Therefore, we suggest that meropenem and piperacillin/tazobactam may be used as first-choice regimens for the treatment of pediatric FN patients.

A previous meta-analysis[16] evaluated carbapenems versus alternative β-lactams for adult FN and showed that meropenem and imipenem/cilastatin monotherapy appeared to be better alternatives for FN treatment than the β-lactams. Another published meta-analysis[18] indicated that ceftazidime, pipera-

Table 2

OR and 95% CI for the comparative efficacy of antipseudomonal β-lactams for the treatment success without modification of pediatric febrile neutropenia.

CFPM	1.08 (0.73, 1.60)	1.47 (0.37, 5.74)	0.99 (0.57, 1.74)		1.38 (0.81, 2.36)	
1.06 (0.59, 2.00)	P/T	1.72 (0.27, 10.96)		1.01 (0.59, 1.72)	0.77 (0.37, 1.59)	0.65 (0.28, 1.51)
1.54 (0.76, 3.30)	1.45 (0.74, 2.98)	MEPM	0.96 (0.57, 1.63)			
1.16 (0.52, 2.39)	1.07 (0.44, 2.49)	0.73 (0.30, 1.74)	CAZ			
1.10 (0.29, 3.31)	1.01 (0.37, 2.65)	0.68 (0.19, 2.25)	0.93 (0.26, 3.40)	C/S		
1.11 (0.42, 3.11)	1.05 (0.40, 2.78)	0.72 (0.23, 2.49)	1.01 (0.30, 3.09)	1.04 (0.27, 4.74)	CZOP	
0.68 (0.15, 3.20)	0.64 (0.16, 2.72)	0.44 (0.09, 2.41)	0.59 (0.12, 3.43)	0.63 (0.13, 4.16)	0.61 (0.11, 3.91)	I/C

The lower triangle (in grey) shows summary ORs (95% CIs) derived in network meta-analysis (taking into account both the direct and indirect evidence) for the comparison of the drug in the row versus the drug in the column as reference. In contrast, the upper triangle (in white) shows summary ORs (95% CIs) derived in traditional pairwise meta-analysis (taking into account direct evidence only) for the comparison of the drug in the column versus the drug in the row as reference. White spaces indicate lack of direct evidence for the given comparison.

C/S = cefoperazone/sulbactam, CAZ = ceftazidime, CFPM = cefepime, CI = confidence interval, CZOP = cefozopran, I/C = imipenem/cilastatin, MEPM = meropenem, OR = odds ratio, P/T = piperacillin/tazobactam.

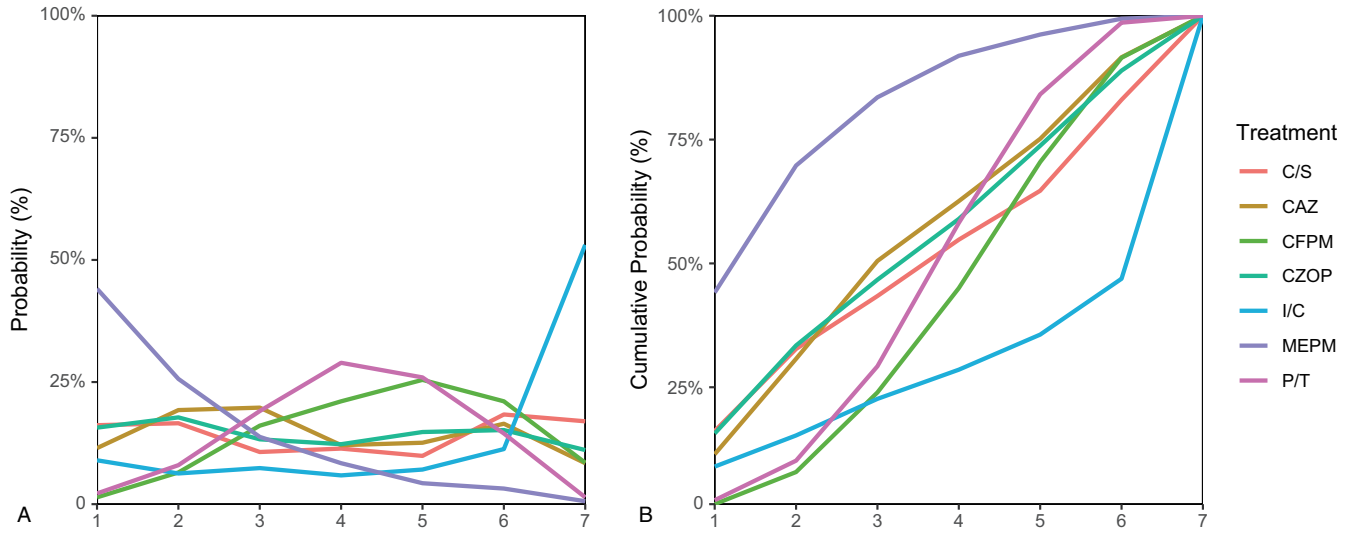

Figure 4. Rankograms and surface under the cumulative ranking curve (SUCRA) plots of treatment success. (A) Rankograms, (B) Cumulative ranking probability plots. C/S = cefoperazone/sulbactam, CAZ = ceftazidime, CFPM = cefepime, CZOP = cefozopran, I/C = imipenem/cilastatin, MEPM = meropenem, P/T = piperacillin/tazobactam.

cillin/tazobactam, imipenem/cilastatin, and meropenem appear to be suitable antibiotics for monotherapy. In the present study, we assessed 2 fourth-generation β-lactams, cefepime and cefozopran. These antibiotics were associated with a lower treatment success rate in the main analysis, without considerable significance. Only 1 included trial evaluated imipenem/cilastatin, and the relative efficacy of imipenem/cilastatin was inconclusive. Further research is required to prove the efficacy of cefoperazone/sulbactam and imipenem/cilastatin.

Currently, clinicians still lack evidence-based guidelines on the selection of the antipseudomonal β-lactams for the treatment of pediatric FN. Thus, while choosing the therapeutic strategy, clinicians should consider all the clinically relevant factors, including microbial sensitivity and comorbidities. In addition, local issues in antibiotic therapy such as epidemiology, pattern of susceptibility, and drug resistance should be considered. A major advantage of our study is the inclusion of substantial comprehensiveness of RCTs that assessed pediatric FN patients

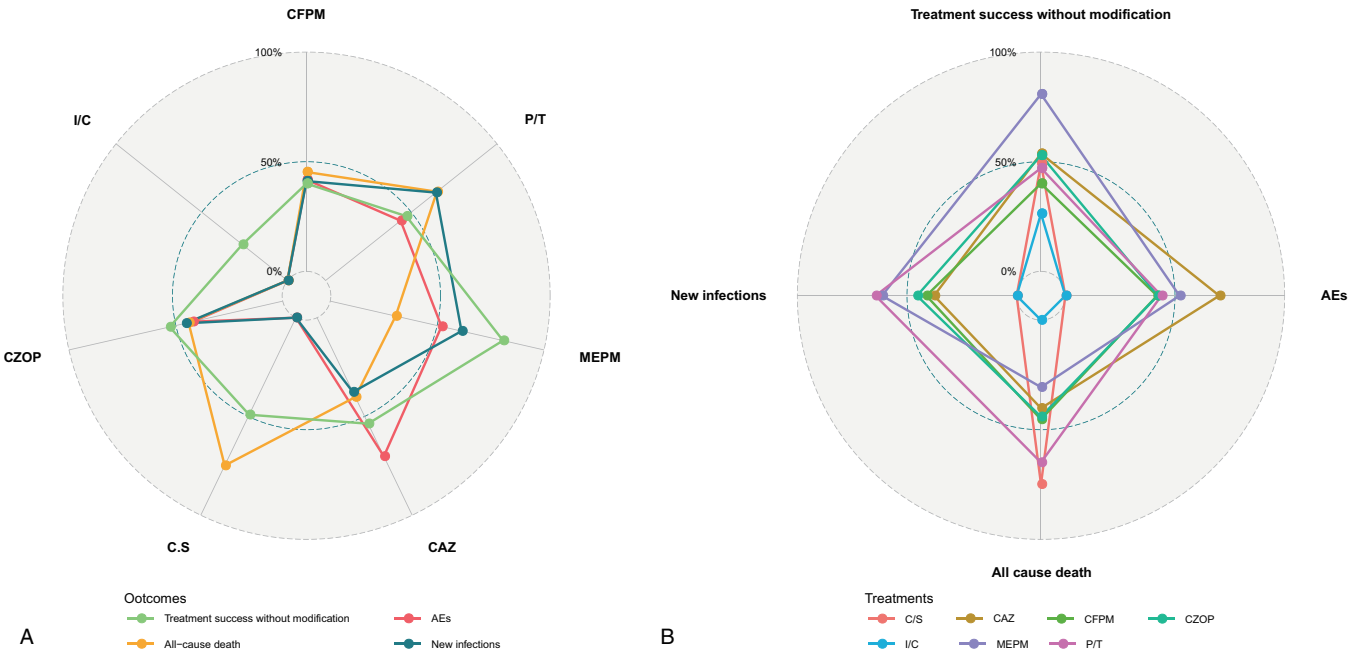

Figure 5. Multidimensional cluster analysis plots. The different colors lines represent different types of antipseudomonal β-lactams. (A) Cluster based on treatment. (B) Cluster based on outcomes. C/S = cefoperazone/sulbactam, CAZ = ceftazidime, CFPM = cefepime, CZOP = cefozopran, I/C = imipenem/cilastatin, MEPM = meropenem, P/T = piperacillin/tazobactam.

as compared to the previous reviews. Previous studies included the patients of all age groups, and their results should be applied to the pediatric age group with caution. Therefore, the present work is the latest completed evaluation of treatment options for efficacy and safety outcomes in pediatric patients. Furthermore, network meta-analysis compares multiple optional antipseudomonal β-lactams, even if there are only a small number of available trials.

This study has some limitations. The open-label and "unclear" methodology study design in most of the included studies may have led to performance and detection biases. The definitions of neutropenic fever and treatment success without modification in each trial were not completely consistent. Premature modification of antibiotics may also lead to treatment failure, and it was difficult to distinguish whether the treatment failure was a function of outright failure in some trials. Finally, there was substantial heterogeneity with regard to designs among some comparisons of the traditional pairwise meta-analysis, which may be a result of high variability in the dose and duration of each drug used. Other potential explanatory factors, such as patient characteristics or study design, have been previously evaluated, but they were not the source of heterogeneity. In addition, considering heterogeneity, our confidence in the quality of the evidence was low to moderate. On the contrary, we could not determine the most effective dose, route of administration, and duration of therapy for each treatment owing to the relatively small sample size, which resulted in insufficient statistical power. Evaluation of each antibiotic regimen without consideration of dosage might introduce some bias.

5. Conclusion

In summary, we performed a systematic review and network meta-analysis to compare the optional antipseudomonal β-lactam monotherapies in pediatric FN patients, including 18 RCTs covering 2517 pediatric patients. The results showed that there was no significant difference in the outcomes of treatment success, all AEs, all-cause mortality, and new infections among these optional antipseudomonal β-lactams. However, based on the results of Bayesian rank probability, meropenem and piperacillin/tazobactam were associated with a higher treatment success rate and a comparable safety profile. Our research should be considered as crucial evidence to help make clinical decisions while choosing an appropriate antipseudomonal β-lactam regimen for the treatment of pediatric FN patients. Considering the quality and sample size of the included studies, well-designed and high-quality RCTs with larger sample sizes are needed to confirm our findings.

Author contributions

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References

[1] Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 1966;64:328–40.
[2] Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56–93.
[3] Masaoka T. Evidence-based recommendations for antimicrobial use in febrile neutropenia in Japan: executive summary. Clin Infect Dis 2004;39 (Suppl 1):S49–52.
[4] Horita N, Shibata Y, Watanabe H, Namkoong H, Kaneko T. Comparison of antipseudomonal β-lactams for febrile neutropenia empiric therapy: systematic review and network meta-analysis. Clin Microbiol Infect 2017;23:723–9.
[5] Paul M, Yahav D, Bivas A, Fraser A, Leibovici L. Anti-pseudomonal β-lactams for the initial, empirical, treatment of febrile neutropenia: comparison of β-lactams. Cochrane Database Syst Rev 2010; CD005197.
[6] Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 1993;328:1323–32.
[7] Bate J, Gibson F, Johnson E, et al. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients (NICE Clinical Guideline CG151). Arch Dis Child Educ Pract Ed 2013;98:73–5.
[8] Sung L, Phillips R, Lehrnbecher T. Time for paediatric febrile neutropenia guidelines - children are not little adults. Eur J Cancer 2011;47:811–3.
[9] Baden LR, Swaminathan S, Angarone M, et al. Prevention and treatment of cancer-related infections, version 2.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2016;14:882–913.
[10] Baden LR, Bensinger W, Angarone M, et al. Prevention and treatment of cancer-related infections. J Natl Compr Canc Netw 2012;10:1412–45.
[11] Tärnberg M, Nilsson LE, Dowzicky MJ. Antimicrobial activity against a global collection of skin and skin structure pathogens: results from the Tigecycline Evaluation and Surveillance Trial (T E S T), 2010–2014. Int J Infect Dis 2016;49:141–8.
[12] Fritsche TR, Sader HS, Jones RN. Comparative activity and spectrum of broad-spectrum β-lactams (cefepime, ceftazidime, ceftriaxone, piperacillin/tazobactam) tested against 12,295 staphylococci and streptococci: report from the SENTRY antimicrobial surveillance program (North America: 2001–2002). Diagn Microbiol Infect Dis 2003;47:435–40.
[13] Tamma PD, Rodriguez-Bano J. The use of noncarbapenem β-lactams for the treatment of extended-spectrum β-lactamase infections. Clin Infect Dis 2017;64:972–80.
[14] Sheu CC, Lin SY, Chang YT, Lee CY, Chen YH, Hsueh PR. Management of infections caused by extended-spectrum β-lactamase-producing Enterobacteriaceae: current evidence and future prospects. Expert Rev Anti Infect Ther 2018;16:205–18.
[15] Karaiskos I, Giamarellou H. Carbapenem-sparing strategies for ESBL producers: when and how. Antibiotics 2020;9:61.
[16] Tang X, Chen L, Li Y, Jiang J, Li X, Liang X. Carbapenems versus alternative β-lactams monotherapy or in combination for febrile neutropenia: systematic review and meta-analysis of randomized controlled trial. Medicine 2020;99:e22725.
[17] Lan SH, Chang SP, Lai CC, Lu LC, Tang HJ. Efficacy and safety of cefoperazone-sulbactam in empiric therapy for febrile neutropenia: a systemic review and meta-analysis. Medicine 2020;99:e19321.
[18] Paul M, Yahav D, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother 2006;57:176–89.
[19] Manji A, Lehrnbecher T, Dupuis LL, Beyene J, Sung L. A systematic review and meta-analysis of anti-pseudomonal penicillins and carbapenems in pediatric febrile neutropenia. Support Care Cancer 2012;20:2295–304.
[20] Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality of evidence from a network meta-analysis. PLoS One 2014;9:e99682.

[21] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84.
[22] Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Available at: www.training.cochrane.org/handbook. Accessed January 20, 2021.
[23] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[24] Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019;22:153–60.
[25] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[26] Crainiceanu CM, Goldsmith AJ. Bayesian functional data analysis using WinBUGS. J Stat Softw 2010;32:i11.
[27] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163–71.
[28] Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. Int J Epidemiol 2013;42: 332–45.
[29] Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods 2012;3:98–110.
[30] Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010;29:932–44.
[31] Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8:e76654.
[32] Hughes WT, Pizzo PA, Wade JC, Armstrong D, Webb CD, Young LS. Evaluation of new anti-infective drugs for the treatment of febrile episodes in neutropenic patients. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis 1992;15(Suppl 1):S206–15.
[33] Society IH. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. Report of a consensus panel. J Infect Dis 1990;161:397–401.
[34] Aamir M, Abrol P, Sharma D, Punia H. A clinical evaluation of efficacy and safety of cefepime monotherapy versus piperacillin-tazobactam in patients of paediatric age group with febrile neutropenia in a tertiary care centre of north India. Trop Doct 2015;46:142–8.
[35] Chuang YY, Hung IJ, Yang CP, Jiang TH, Lin TY, Huang YC. Cefepime versus ceftazidime as empiric monotherapy for fever and neutropenia in children with cancer. Pediatr Infect Dis J 2002;21:203–9.
[36] Corapcioglu F, Sarper N, Zengin E. Monotherapy with piperacillin/tazobactam versus cefepime as empirical therapy for febrile neutropenia in pediatric cancer patients: a randomized comparison. Pediatr Hematol Oncol 2006;23:177–86.
[37] Demirkaya M, Celebi S, Sevinir B, Hacımustafaoglu M. Randomized comparison of piperacillin-tazobactam plus amikacin versus cefoperazone-sulbactam plus amikacin for management of febrile neutropenia in children with lymphoma and solid tumors. Pediatr Hematol Oncol 2013;30:141–8.
[38] Ferdosian F, Ghiliyan R, Hashemi A, Akhondzadeh B, Gholampoor E. Comparing the efficacy of ceftazidime and meropenem in treatment of febrile neutropenia in pediatric patients with cancer. Iran J Ped Hematol Oncol 2013;3:103–7.
[39] Fleischhack G, Hartmann C, Simon A, et al. Meropenem versus ceftazidime as empirical monotherapy in febrile neutropenia of paediatric patients with cancer. J Antimicrob Chemother 2001;47: 841–53.
[40] Ichikawa M, Suzuki D, Ohshima J, et al. Piperacillin/tazobactam versus cefozopran for the empirical treatment of pediatric cancer patients with febrile neutropenia. Pediatr Blood Cancer 2011;57: 1159–62.
[41] Karaman S, Vural S, Yildirmak Y, Emecen M, Erdem E, Kebudi R. Comparison of piperacillin tazobactam and cefoperazone sulbactam monotherapy in treatment of febrile neutropenia. Pediatr Blood Cancer 2012;58:579–83.
[42] Kebudi R, Görgün O, Ayan I, Gürler N, Akici F, Töreci K. Randomized comparison of cefepime versus ceftazidime monotherapy for fever and neutropenia in children with solid tumors. Med Pediatr Oncol 2001; 36:434–41.
[43] Kobayashi R, Sano H, Matsushima S, et al. Meropenem versus piperacillin/tazobactam for febrile neutropenia in pediatric patients: efficacy of piperacillin/tazobactam as a 1-h drip infusion four times a day. Int J Hematol 2021;113:430–5.
[44] Kutluk T, Kurne O, Akyüz C, et al. Cefepime vs. Meropenem as empirical therapy for neutropenic fever in children with lymphoma and solid tumours. Pediatr Blood Cancer 2004;42:284–6.
[45] Mustafa MM, Carlson L, Tkaczewski I, McCracken GH, Buchanan GR. Comparative study of cefepime versus ceftazidime in the empiric treatment of pediatric cancer patients with fever and neutropenia. Pediatr Infect Dis J 2001;20:362–9.
[46] Oguz A, Karadeniz C, Citak EC, Cil V, Eldes N. Experience with cefepime versus meropenem as empiric monotherapy for neutropenia and fever in pediatric patients with solid tumors. Pediatr Hematol Oncol 2006;23:245–53.
[47] Sano H, Kobayashi R, Suzuki D, Kishimoto K, Yasuda K, Kobayashi K. Comparison between piperacillin/tazobactam and cefepime monotherapies as an empirical therapy for febrile neutropenia in children with hematological and malignant disorders: a prospective, randomized study. Pediatr Blood Cancer 2015;62:356–8.
[48] Sarashina T, Kobayashi R, Yoshida M, et al. A randomized trial of cefozopran versus cefepime as empirical antibiotic treatment of febrile neutropenia in pediatric cancer patients. Pediatr Blood Cancer 2014; 61:1992–5.
[49] Sezgin G, Acipayam C, Ozkan A, Bayram I, Tanyeli A. Meropenem versus piperacillin-tazobactam as empiric therapy for febrile neutropenia in pediatric oncology patients. Asian Pac J Cancer Prev 2014;15: 4549–53.
[50] Uygun V, Karasu GT, Ogunc D, Yesilipek A, Hazar V. Piperacillin/tazobactam versus cefepime for the empirical treatment of pediatric cancer patients with neutropenia and fever: a randomized and open-label study. Pediatr Blood Cancer 2009;53:610–4.
[51] Vural S, Erdem E, Gulec SG, Yildirmak Y, Kebudi R. Imipenem-cilastatin versus piperacillin-tazobactam as monotherapy in febrile neutropenia. Pediatr Int 2010;52:262–7.
[52] Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;342:D549.