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# Piperacillin-tazobactam versus Cefepime Monotherapy in Pediatric Patients with Febrile Neutropenia: a Systematic Review and Meta-Analysis

**Bernardo Luís Giacomelli Fernandes**

bernardolgf1@gmail.com

University of Brasília

**Allan Joseph**

University of Western Australia

**Vítor Honorato Andriazzi**

University of Brasília

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## Abstract

# Purpose

To evaluate whether piperacillin-tazobactam therapy, compared with cefepime monotherapy, results in a significant difference in treatment success, mortality and duration outcomes in pediatric patients with febrile neutropenia (FN).

# Methods

A systematic review and meta-analysis of Randomized Controlled Trials (RCTs) was conducted following PRISMA guidelines. Databases (PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL) were searched up to February 3rd. We only included studies of pediatric patients with FN comparing piperacillin-tazobactam to cefepime monotherapy. Risk of bias was assessed using Cochrane RoB 2 tool. Meta-analysis was performed using a random-effects model to calculate Risk Ratios (RR) and Mean Differences (MD).

# Results

Five RCTs involving 470 episodes were included. The pooled analysis for treatment success showed no statistically significant difference between groups (RR = 1.02; 95% CI [0.89; 1.18]; *P = 0.7608*) with low heterogeneity ($I^2$ = 0.0%). No significant differences for mortality (RR = 2.12; 95% CI [0.63; 7.14]; P = 0.23; $I^2$ = 0.0%). Duration of treatment was 0.9 day shorter for cefepime group (MD = 0.9 day; 95% CI [0.2; 1.6]; P < 0.1; $I^2$ = 0%).

# Conclusions

No statistically significant difference was found in treatment success or mortality between the groups. Patients receiving cefepime had a treatment duration 0.9 days shorter than those receiving piperacillin–tazobactam, although this finding should be interpreted with caution. Overall, the available evidence remains limited. Further randomized controlled trials are needed to better determine potential differences in treatment success, mortality, and duration between the drugs.

## What is known and what is new?

- **What is known:** Cefepime and piperacillin-tazobactam are widely utilized as empirical monotherapy for febrile neutropenia, but evidence regarding their comparative clinical efficacy and safety in children remains inconclusive.

- **What is new:** This meta-analysis quantifies differences in treatment success, mortality and duration of treatment outcomes in pediatric patients with febrile neutropenia.

# 1. Introduction

## 1.1 Background

Febrile neutropenia is a frequent and life-threatening complication of chemotherapy and hematopoietic stem cell transplantation in children and adults. Due to impaired innate immune defenses, bacterial infections can progress rapidly with minimal clinical signs, necessitating the immediate administration of broad-spectrum intravenous empiric therapy.

## 1.2 Rationale and knowledge gap

Cefepime and piperacillin–tazobactam are the primary antipseudomonal β-lactams used in pediatric FN. Although both provide robust Gram-negative coverage, they differ significantly: piperacillin–tazobactam offers additional anaerobic activity, whereas cefepime is often preferred for its strong antipseudomonal efficacy. However, cefepime is associated with potential neurotoxicity, while piperacillin–tazobactam may contribute to renal complications, particularly when used with other nephrotoxic agents. While research on the effectiveness of cefepime and piperacillin-tazobactam for adults is well documented in the literature, studies designed to evaluate this usage in children are still sparse. Existing evidence in children across studies is inconclusive, and a systematic synthesis is required to determine if clinical outcomes differ between these two drugs.

## 1.3 Objective

The objectives of this review are (i) to compare treatment success between piperacillin–tazobactam and cefepime monotherapy in pediatric patients with FN using pooled effect estimates and to critically appraise the published evidence; (ii) to compare mortality rates between the two groups; (iii) to evaluate duration of treatment based on the drug used.

# 2. Methods

## 2.1 Protocol and Registration

The review was performed in line with the Cochrane Collaboration [1] and PRISMA [2] guidelines, and was registered in PROSPERO (CRD420261296621). The search protocol can be found there.

## 2.2 Literature search and information sources

A structured search was applied to PubMed, Embase, Scopus, Web of Science, and Cochrane (CENTRAL). The search was last conducted on February 3rd, 2026. The search strategy focused on pediatric patients, febrile neutropenia, piperacillin-tazobactam, and cefepime. The full search strategy is available in the footnote.

## 2.3 Eligibility criteria

Inclusion criteria were: (1) Randomized Controlled Trials (RCTs) or cohort studies; (2) Pediatric patients with febrile neutropenia; (3) Intervention: piperacillin–tazobactam; (4) Comparator: cefepime monotherapy. Studies were grouped for synthesis based on clinical outcomes (success of treatment, mortality, duration).

## 2.4 Study selection and Data extraction

Two reviewers independently screened titles and abstracts and assessed full texts. Data extraction included the first author, year, population characteristics, and main outcomes recorded on an Excel template. Data extracted from studies are available as a supplementary file.

## 2.5 Quality assessment

Risk of bias for RCTs was assessed independently by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool [3]. Domains included randomization, deviations from intended interventions, missing data, outcome measurement, and selection of reported results.

## 2.6 Data synthesis and Statistical analysis

Meta-analyses were conducted using a random-effects model (Restricted Maximum Likelihood - REML estimator) in R software [4] (Version 4.5.2) with packages meta, rstudioapi and readxl. The R code script is available as a supplementary file.

The effect measures were Risk Ratio (RR) for binary outcomes (success of treatment and mortality) and Mean Difference (MD) for continuous outcomes (duration of treatment). When the studies did not directly report mean and standard deviation, they were estimated using median, range, and sample size, as recommended by Wan et al. (2014). Heterogeneity was evaluated with the Cochran Q test and $I^2$ statistics; $p < 0.10$ or $I^2 > 25\%$ were considered significant for heterogeneity. Data extracted from studies were displayed in tables, and the results of statistical analyses were displayed in forest plots.

## 2.7 Certainty of findings

Certainty of findings was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [6] system, by means of GRADEpro software [7].

## 2.8 Publication bias

Publication bias was planned to be assessed using funnel plots and Egger’s regression test; however, these analyses were not possible due to the inclusion of fewer than 10 studies, in accordance with Cochrane Collaboration recommendations [1].

## 2.9 Sensitivity analysis

Sensitivity was evaluated using a leave-one-out analysis for outcomes in which a single study disproportionately influenced the pooled effect estimate.

# 3. Results

# 3.1 Search results

The search identified 397 studies. After screening 286 titles and 51 abstracts, 27 articles were assessed for full-text eligibility. Five studies met the final inclusion criteria. Reasons for exclusion at the full-text stage included non-monotherapy, non-pediatric populations, and data not stratified by treatment group. The search results are summarized in Fig. 1.

**3.2 Characteristics of the included studies** A total of 470 episodes from 221 participants were included across 5 RCTs (Aamir et al. 2015 [8]; Corapcioglu et al. 2006 [9]; Sano et al. 2014 [10]; Uygun et al. 2009 [11]; Kebudi et al. 2005 [12]). The details about each study are summarized in Table 1 for piperacillin-tazobactan group and Table 2 for cefepime group.

Table 1
Study characteristics for piperacillin-tazobactam group.

| **Authors** | **Aamir et al. (2015)** | **Corapcioglu et al. (2006)** | **Sano et al. (2014)** | **Uygun et al. (2009)** | **Kebudi et al. (2005)** |
|---|---|---|---|---|---|
| Number of episodes | 20 | 25 | 103 | 65 | 20 |
| Number of patients | 20 | 14 | 27 | 35 | 16 |
| Mean age (years) | 6 | 8.4 | 10 | 5.3 | 11.8 |
| Male sex | 70% | 40% | 50% | 52% | NR |
| Drug dosage | 100 mg/kg/dose every 8 h | 80 mg/kg piperacillin/10 mg/kg tazobactam every 6 h | 337.5 mg/kg/day in three portions | 80 mg/kg piperacillin/10 mg/kg tazobactam every 6 h | NR |
| Success of treatment | 15 | 14 | 64 | 39 | 9 |
| Mortality | 4 | 0 | 1 | 2 | 0 |
| Mean treatment duration (days) | NR | 10.8 | 10 | 14.2 | NR |
| Country | India | Turkey | Japan | Turkey | UK |

Table 2
Study characteristics for cefepime group.

| Authors | Aamir et al. (2015) | Corapcioglu et al. (2006) | Sano et al. (2014) | Uygun et al. (2009) | Kebudi et al. (2005) |
|---|---|---|---|---|---|
| Number of episodes | 20 | 25 | 110 | 62 | 20 |
| Number of patients | 20 | 14 | 26 | 34 | 15 |
| Mean age (years) | 6.8 | 8.4 | 11 | 5.6 | 11.8 |
| Male sex | 60% | 40% | 50% | 48% | NR |
| Drug dosage | 50 mg/kg/dose every 8 h | 50 mg/kg every 8h | 100 mg/kg/day in four portions | 50 mg/kg every 8 h | NR |
| Success of treatment | 16 | 12 | 65 | 38 | 11 |
| Mortality | 2 | 0 | 0 | 1 | 0 |
| Mean treatment duration (days) | NR | 11.8 | 9 | 12.8 | NR |
| Country | India | Turkey | Japan | Turkey | UK |

# 3.3 Risk of bias outcomes

The overall risk of bias based on Cochrane Risk of Bias 2 (RoB 2) tool [3] was judged as "low" for four studies and "some concerns" for Kebudi et al. (2005). The detailed risk of bias is presented in Fig. 2.

# 3.4 Primary outcome: Treatment Success

- RR: 1.02 95% CI 0.89; 1.18 .
- *Statistical significance: z = 0.3, P = 0.7608* .
- *Heterogeneity: $I^2$ = 0.0%; p = 0.9509* .

Across five randomized trials (n = 470), treatment success occurred in 145/233 (62.2%) patients receiving piperacillin–tazobactam and 143/237 (60.3%) receiving cefepime. Pooled analysis showed no statistically significant difference between groups (RR: 1.02 95% CI 0.89; 1.18; P = 0.76), corresponding to an absolute risk difference of + 1.9 percentage points (95% CI − 8.3 to + 9.5). Statistical heterogeneity was negligible ($I^2$ = 0%). These findings are displayed in Fig. 3.

# 3.5 Secondary outcomes

- **Mortality**:

- RR: 2.12 95% CI 0.63; 7.14 .
- *Statistical significance: z = 1.21, P = 0.2273* .
- *Heterogeneity: I² = 0.0%; p = 0.9622* .

Across five randomized trials (n = 470), mortality occurred in 7/233 (3%) patients receiving piperacillin–tazobactam and 3/237 (1.2%) receiving cefepime. Pooled analysis produced an RR of 2.12 (95% CI 0.63–7.14; P = 0.23), corresponding to an absolute risk difference of + 1.7 percentage points (95% CI − 0.4 to + 7.4). Heterogeneity was low (I² = 0%). These results are shown in Fig. 4.

- **Duration of treatment**:
  - MD: 0.9 95% CI 0.2; 1.6 .
  - *Statistical significance: z = 2.44, P < 0.1* .
  - *Heterogeneity: I² = 0.0%; p = 0.5603* .

Three randomized trials (n = 390) reported duration of treatment (days). The pooled mean difference was 0.9 days longer with piperacillin–tazobactam compared with cefepime (MD 0.90, 95% CI 0.20–1.60; Z = 2.44, P ≈ 0.015), indicating a small but statistically significant increase in treatment duration in the piperacillin–tazobactam arm. Statistical heterogeneity was negligible (I² = 0%). These findings are summarized in Fig. 5.

# 3.6 Sensitivity analysis

For duration of treatment, leave-one-out analysis was performed. It showed that the pooled effect was generally stable, with no evidence of heterogeneity in most scenarios. However, exclusion of Sano et al. (2014) resulted in loss of statistical significance (MD 0.07, 95% CI − 2.59 to 2.73), indicating that this study had a substantial influence on the overall estimate. Besides, omission of Uygun et al. (2009) attenuated the effect to non-significance. Removal of Corapcioglu et al. (2006) did not materially change the results. These findings suggest moderate sensitivity of the pooled estimate to individual studies, particularly Sano et al. Figure 6 displays these results.

# 3.7 Publication bias

Publication bias was planned to be assessed using funnel plots and Egger's regression test; however, these analyses were not possible due to the inclusion of fewer than 10 studies.

# 3.8 Certainty of findings

Certainty of findings was assessed using the GRADE system [6]. Once all studies were randomized controlled trials, initial certainty was held as high, and downgraded when necessary. Certainty for success of treatment was graded as 'high'. Certainty for duration of treatment was downgraded by one level to "moderate", owing to noticeable inconsistency in findings for the study by Uyugun et al. (2009).

Certainty for mortality was downgraded by one level to “moderate”, owing to the confidence interval being too broad, encompassing notable risk. These results are summarized in Table 3.

Table 3 - Summary of findings based on GRADE system [6].

| **Outcomes** | **№ of participants (studies) Follow-up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
|---|---|---|---|---|---|
| | | | | **Risk with Cefepime** | **Risk difference with Piperacillin-tazobactam** |
| Success of treatment | 470 (5 RCTs) | ⨁⨁⨁⨁ High | **RR 1.02** (0.89 to 1.18) | 599 per 1,000 | **12 more per 1,000** (from 66 fewer to 108 more) |
| Mortality | 470 (5 RCTs) | ⨁⨁⨁◯ Moderate[a] | **RR 2.12** (0.63 to 7.14) | 13 per 1,000 | **14 more per 1,000** (from 5 fewer to 78 more) |
| Duration of treatment | 390 (3 RCTs) | ⨁⨁⨁◯ Moderate[b] | - | The mean duration of treatment was **10.61** days | MD **0.9 days higher** (0.2 higher to 1.6 higher) |
| ***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).<br>**CI**: confidence interval; **MD**: mean difference; **RR**: risk ratio | | | | | |
| **GRADE Working Group grades of evidence** | | | | | |
| **High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect. | | | | | |
| **Moderate certainty**: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. | | | | | |
| **Low certainty**: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. | | | | | |
| **Very low certainty**: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. | | | | | |

**Explanations**

a. The confidence interval (CI) range is broad, encompassing notable risk.

b. The data in Uyugun et al. (2009) (mean and standard deviation) differ moderately from the other studies

# 4. Discussion

## 4.1 Interpretation of results

The pooled RCT data did not show a statistically significant difference in treatment success between piperacillin–tazobactam and cefepime for pediatric patients with febrile neutropenia.

Although the pooled point estimate suggests higher mortality with piperacillin–tazobactam, the confidence interval is wide and includes no effect; only 10 deaths occurred in total. Therefore, these data do not reliably demonstrate increased (or decreased) mortality. Consequently, the data are insufficient to confirm a difference in mortality. Larger, adequately powered trials are required to establish safety equivalence. In the interim, treatment selection should be guided by local resistance patterns, toxicity profiles, and clinical judgment.

Although the meta-analysis found a statistically significant mean increase of approximately 0.9 days in treatment duration with piperacillin–tazobactam, this result is driven overwhelmingly by a single large trial (which contributed ≈ 93% of the weight). The absolute difference — less than one day — is unlikely to be clinically important in most settings. Moreover, heterogeneity was low, but the dominance of one study raises concerns about robustness. Sensitivity analyses excluding that trial could alter the result. Consequently, these data provide limited evidence of a meaningful difference in treatment duration, and clinicians should interpret this finding in the context of trial methods, local practice patterns, and patient priorities.

## 4.2 Limitations

Limitations include the small number of included studies (k = 5) and episodes (n = 461). Risk of bias was not a concern, once the overall risk for most studies was low, except for Kebudi et al.(2005), which was “some concerns”. For the duration of treatment outcome, the pooled estimate was heavily driven by a single study, which presents a limitation in the finding. The review process has limitations. The literature search was restricted to studies published in English, which may have resulted in language bias and the omission of relevant evidence.

## 4.3 Systematic review and comparison with similar research

Empirical monotherapy with antipseudomonal β-lactams has been evaluated extensively in pediatric febrile neutropenia, and several randomized trials and systematic reviews support broadly comparable efficacy between piperacillin–tazobactam and cefepime. Large randomized, open-label multicenter trials reported similar clinical outcomes for piperacillin–tazobactam versus cefepime, with comparable safety profiles and only minor differences in early clinical success in some studies [13]. This overall concordance between trials is reflected in other systematic reviews and meta-analyses, which generally found no clear superiority of one agent over the other for empirical management of febrile neutropenia in children [14, 15]. Individual trials comparing piperacillin–tazobactam to other regimens such as

cefozopran or ceftriaxone plus gentamicin have likewise tended to show comparable or, in some cases, modestly better outcomes with piperacillin–tazobactam, but the totality of evidence points to an absence of a large, consistent efficacy advantage for any single antipseudomonal β-lactam [16, 17]. These data support the interpretation that both agents are reasonable empirical choices when used as monotherapy in pediatric febrile neutropenia.

Antimicrobial resistance patterns, particularly the prevalence of extended-spectrum β-lactamase (ESBL) producing Enterobacterales, impact the choice and effectiveness of empirical therapy. Several reports have documented a burden of ESBL E. coli and Klebsiella bacteremia in febrile neutropenic children and have shown reduced susceptibility to many β-lactams, arguing that in high-ESBL prevalence settings, monotherapy with piperacillin–tazobactam or cefepime may be inadequate and combination or carbapenem-based strategies should be considered [18, 19]. This microbiologic reality underlines that comparative efficacy observed in trials conducted in low-resistance environments may not generalize to centers with different resistance ecology; local antibiograms should therefore be central to empirical antibiotic policy and interpretation of study results [18, 19].

Combination therapy continues to be a widely used strategy. RCTs and cohort studies in both pediatric and adult populations have examined combinations such as β-lactam plus aminoglycoside, and evidence indicates that combination regimens can be effective, particularly for severe presentations or when resistant gram-negative pathogens are suspected [20, 21]. Specific randomized comparisons have shown that piperacillin–tazobactam performs favorably against ceftriaxone plus gentamicin in hematologic malignancy populations, suggesting there may be clinical scenarios where single-agent broad antipseudomonal β-lactams outperform other combinations [16]. However, combination therapy carries risk, such as toxicity and cost, and the decision should be individualized based on patient severity, prior infections, medical history, and epidemiologic conditions of the hospital [20, 21].

Strategies such as cycling or alternating first-line empirical antibiotics have been proposed and trialed. Programs that did that reported maintained clinical efficacy and suggested a potential to reduce selection pressure for certain resistance mechanisms [22, 23]. Nevertheless, the strength of the evidence is heterogeneous and implementation requires surveillance, acceptance from clinicians and robust infection-control infrastructure. The applicability to pediatric oncology centers should be considered experimentally, not assumed effective [22, 23].

Observational analyses and cohort studies have signaled an increased risk of acute kidney injury when vancomycin is combined with piperacillin–tazobactam when compared with vancomycin plus cefepime in pediatric populations [24, 25]. Such nephrotoxicity should prompt clinicians to weigh the benefits of empirical piperacillin–tazobactam versus cefepime when vancomycin co-administration is anticipated, to consider alternative strategies, and to carefully monitor renal function if it is used [24, 25].

Heterogeneity in clinical practice and patient-level factors further complicates generalization. Surveys of pediatric centers demonstrate marked variability in febrile neutropenia management across regions and institutions, with empirical antibiotic selection strongly influenced by local protocols, clinician

preference, and perceived resistance risks [26, 27]. Documented β-lactam allergy is a frequent determinant of antibiotic choice and can drive the use of broader regimens, which are potentially less effective [28]. Studies evaluating drug utilization show that cefepime monotherapy and piperacillin–tazobactam remain widely used in pediatric oncology [27].

Methodologic syntheses corroborate the practical message that no single antipseudomonal β-lactam has demonstrated clear superiority in pediatric febrile neutropenia. A network meta-analysis and other comparative systematic reviews have tended to find broadly comparable efficacy among major agents (such as cefepime, piperacillin–tazobactam, and carbapenems) without a dominant drug, and reviews of cefepime and piperacillin–tazobactam in children have similarly characterized both drugs as effective and generally well tolerated [14, 15, 29, 30]. Therefore, the findings of this meta-analysis align with the existing literature, but it also emphasizes that aggregated trial data are insufficient to precisely rule out clinically meaningful differences in outcomes such as mortality and success of treatment.

Our findings, which are consistent with prior RCTs and reviews, therefore support continued use of either piperacillin–tazobactam or cefepime as reasonable first-line therapies, while highlighting the need of individualized decision-making evaluating resistance patterns, drug toxicity, and institutional stewardship [13, 14, 16, 31].

## 4.4 Implications

Clinicians can utilize both piperacillin-tazobactam and cefepime based on local antibiograms and patient-specific conditions. Cefepime is a recommended alternative if renal toxicity is a concern, provided it is monitored.

# 5. Conclusion

This meta-analysis did not demonstrate a statistically significant difference in treatment success or mortality between piperacillin–tazobactam and cefepime in pediatric patients with febrile neutropenia. Patients receiving cefepime had a treatment duration 0.9 days shorter than those receiving piperacillin–tazobactam, although this finding was largely driven by a single dominant trial and should be interpreted with caution. Overall, the available evidence remains limited and does not establish equivalence between the two regimens. Further randomized controlled trials are needed to better determine potential differences in treatment success, mortality, and duration.

# Declarations


- **Funding:** The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.
- **Conflicts of Interest:** The authors have no relevant financial or non-financial interests to disclose.
- **Data Availability:** Data extracted from studies and R code script are available as supplementary files.

- **Full search string:** ("febrile neutropenia" OR "neutropenic fever" OR "fever and neutropenia" OR ("fever" AND neutropenia) OR "neutropenic sepsis") AND (pediatric OR paediatric OR child OR children OR adolescent OR infant OR neonate OR newborn OR "young patient*") AND (cefepime) AND ("piperacillin tazobactam" OR "piperacillin-tazobactam" OR pip-tazo OR piptazo OR TZP OR PTZ).
- **CRediT authorship contribution statement:** BLGF: Writing — review & editing, Writing — original draft, Investigation, Supervision, Project administration, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization, Software. AJ: Writing — review & editing, Resources, Methodology, Visualization, Methodology, Data curation. VHA: Writing — review & editing, Resources, Methodology, Formal analysis, Data curation, Conceptualization, Software.

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# Figures

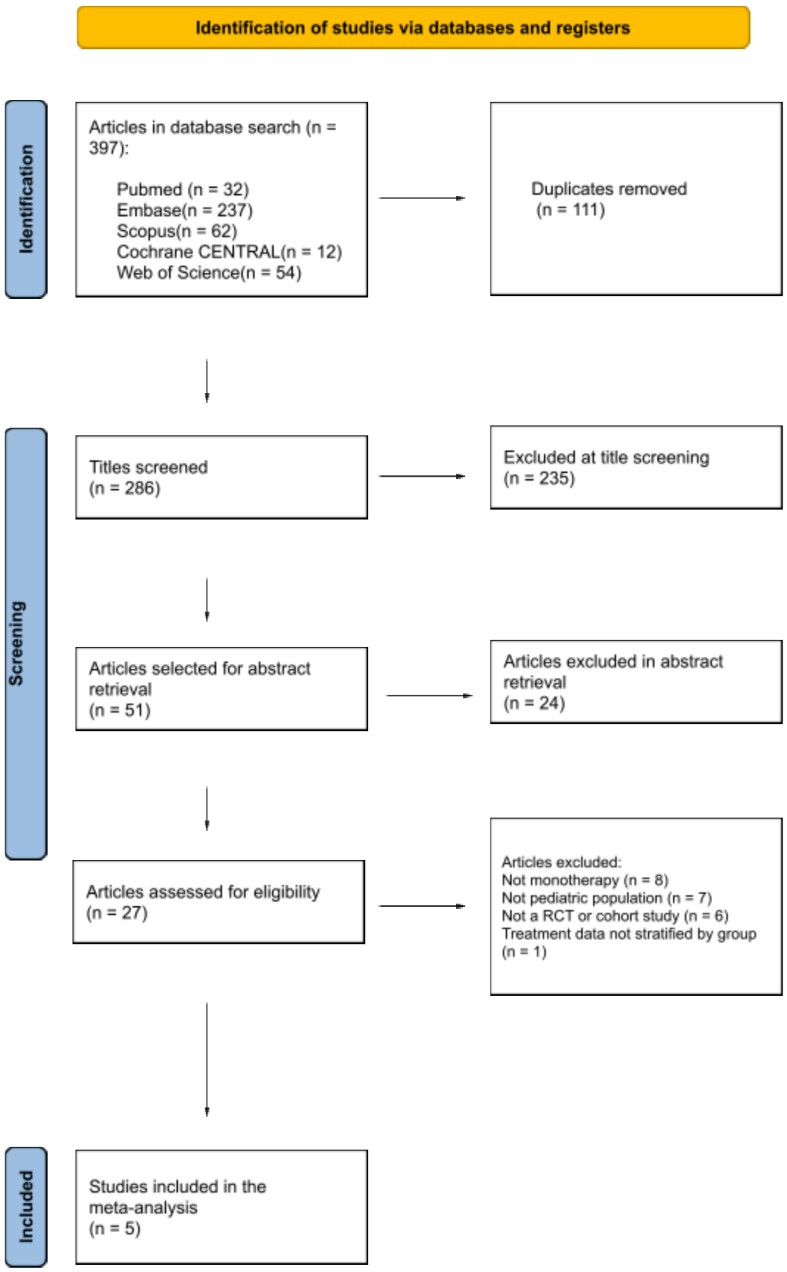



**Figure 1**

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [2] flow diagram of included studies.

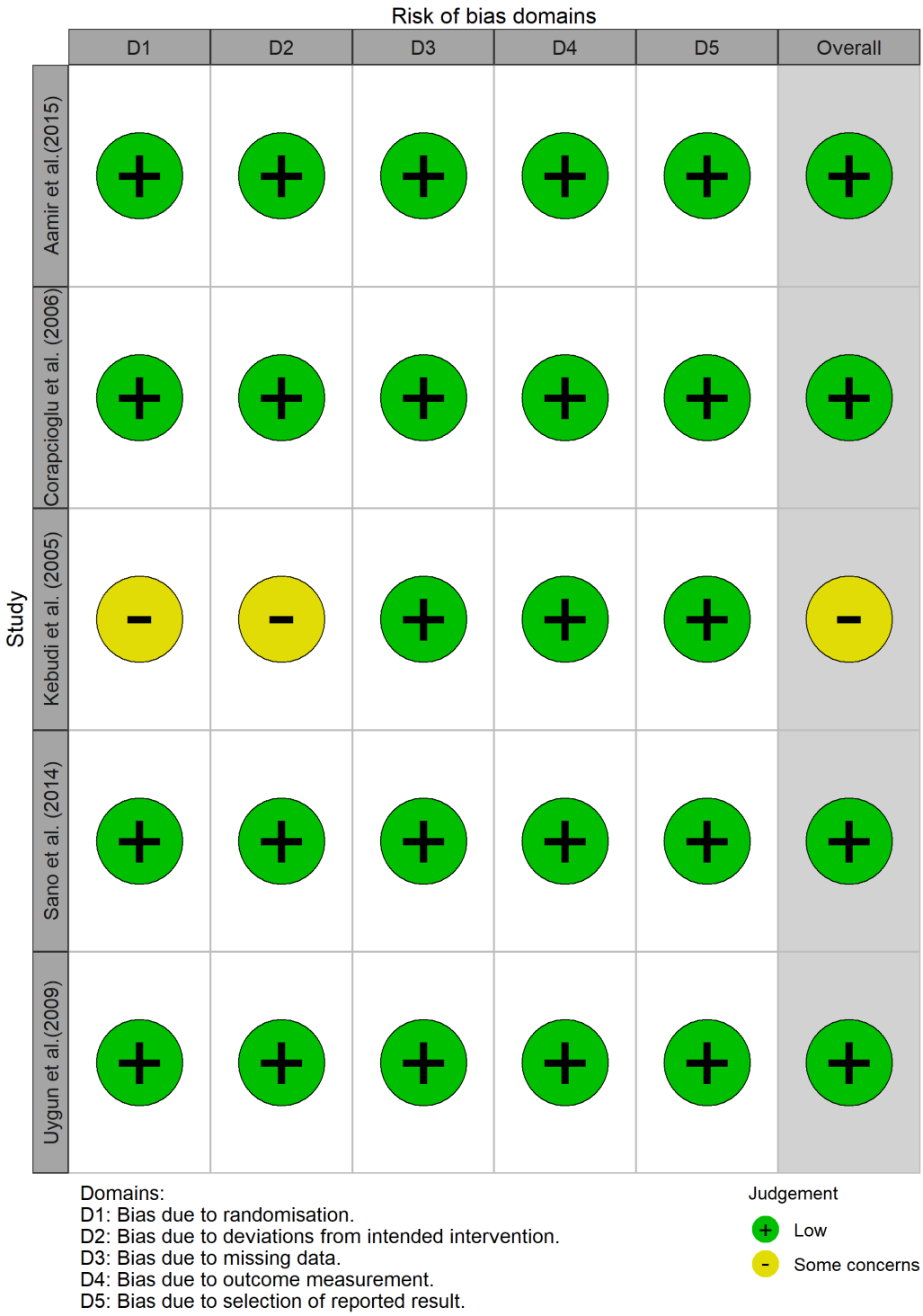
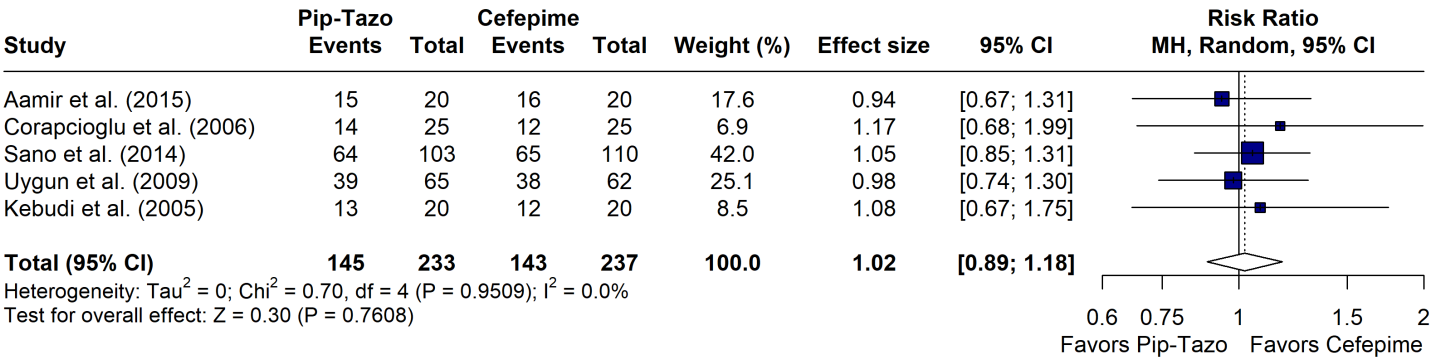


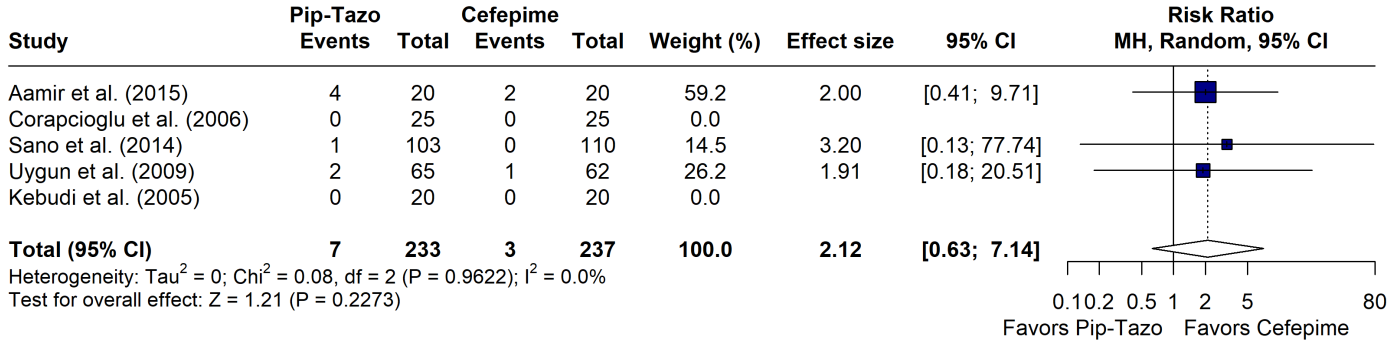

**Figure 2**

Risk of bias plot.



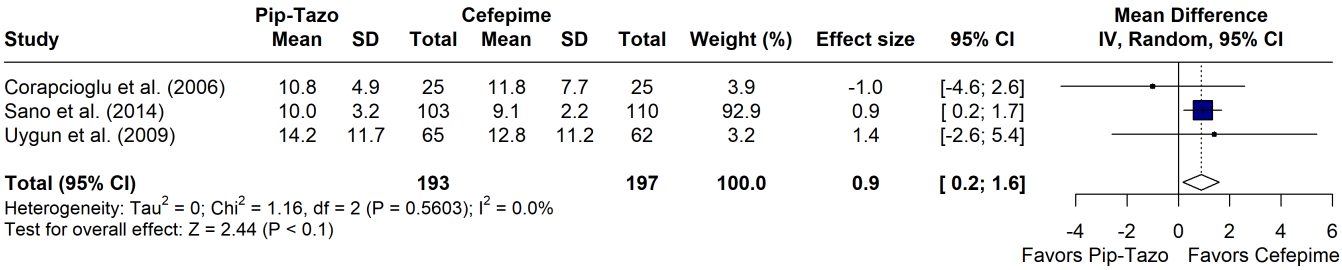

## Figure 3

Forest plot of success of treatment.




## Figure 4

Forest plot of mortality owing to infections.




## Figure 5

Forest plot of duration of treatment.

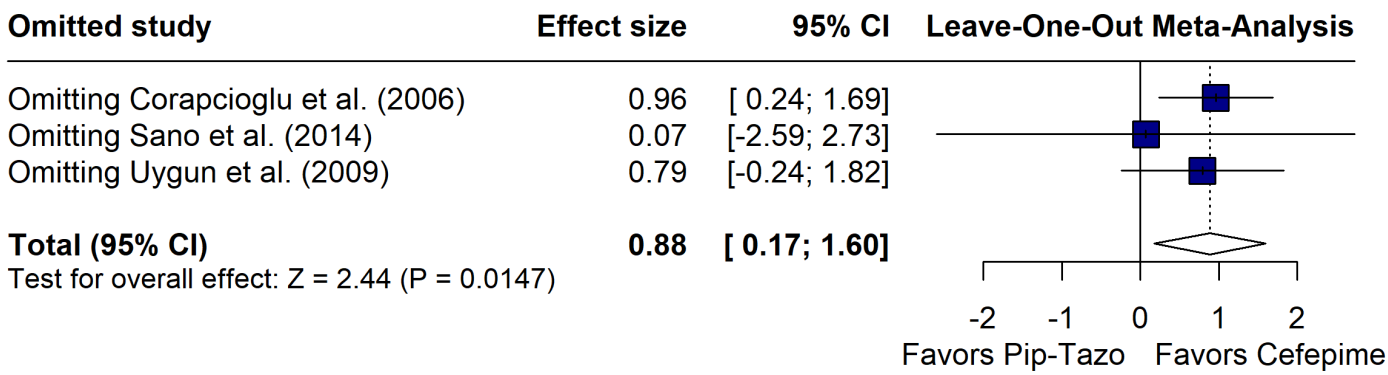



**Figure 6**

Forest plot of the leave-one-out analysis for duration of treatment.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Binaryoutcomesmetaanalysisandforestplottextformat.txt
- Continuousoutcomesmetaanalysisandforestplottextformat.txt
- ExtracteddataPiptazovscefepimemetaanalysis1.xlsx