

The Dose-Dependent Efficacy of Cefepime in the Empiric Management of Febrile Neutropenia: A Systematic Review and Meta-Analysis

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Background. Despite reports questioning its efficacy, cefepime remains a first-line option in febrile neutropenia. We aimed to re-evaluate the role of cefepime in this setting.

Methods. We searched the PubMed and EMBASE databases to identify randomized comparisons of (1) cefepime vs alternative monotherapy or (2) cefepime plus aminoglycoside vs alternative monotherapy plus aminoglycoside, published until November 28, 2016.

Results. Thirty-two trials, reporting on 5724 patients, were included. Clinical efficacy was similar between study arms ($P = .698$), but overall mortality was greater among cefepime-treated patients (risk ratio [RR] = 1.321; 95% confidence interval [CI], 1.035–1.686; $P = .025$). Also of note, this effect seemed to stem from trials using low-dose (2 grams/12 hours, 100 mg/kg per day) cefepime monotherapy (RR = 1.682; 95% CI, 1.038–2.727; $P = .035$). Cefepime was also associated with increased mortality compared with carbapenems (RR = 1.668; 95% CI, 1.089–2.555; $P = .019$), a finding possibly influenced by cefepime dose, because carbapenems were compared with low-dose cefepime monotherapy in 5 of 9 trials. Treatment failure in clinically documented infections was also more frequent with cefepime (RR = 1.143; 95% CI, 1.004–1.300; $P = .043$). Toxicity-related treatment discontinuation was more common among patients that received high-dose cefepime ($P = .026$), whereas low-dose cefepime monotherapy resulted in fewer adverse events, compared with alternative monotherapy ($P = .009$).

Conclusions. Cefepime demonstrated increased mortality compared with carbapenems, reduced efficacy in clinically documented infections, and higher rates of toxicity-related treatment discontinuation. The impact of cefepime dosing on these outcomes is important, because low-dose regimens were associated with lower toxicity at the expense of higher mortality.

Keywords. cancer; cefepime; dose; febrile; neutropenia.

Cefepime is a fourth-generation cephalosporin with a broad spectrum of in vitro activity [1, 2] that was first approved for clinical use in 1996 [3]. Shortly afterwards, the US Food and Drug Administration (FDA) approved cefepime for the empiric treatment of febrile neutropenia, and cefepime is still recommended as a first-line option for this indication by organizations, such as the Infectious Diseases Society of America, the European Society for Medical Oncology, and the Japan Febrile Neutropenia Study Group [4–6]. However, the safety and efficacy of cefepime therapy in febrile neutropenia has been controversial.

Specifically, between 2005 and 2010, a series of meta-analyses demonstrated increased overall mortality among patients receiving cefepime, both in and outside the setting of febrile neutropenia [7–9]. Although a specific cause was never identified, serious concerns were raised, and the FDA (in cooperation with the manufacturer) conducted an extensive meta-analysis, including previously unpublished data, and concluded that cefepime administration was not associated with increased mortality [3]. Nonetheless, another meta-analysis that was published shortly afterwards, and incorporated the mortality figures from the FDA review, again detected increased overall mortality among cefepime-treated patients with febrile neutropenia [9]. Seven years have elapsed since then, but the controversy has yet to be resolved. The aim of the present meta-analysis was to reassess the efficacy and safety of cefepime in the management of febrile neutropenia and to investigate the impact of dosing regimens on outcomes, given the frequent use of low-dose (2 grams/12 hours, 100 mg/kg per day) cefepime therapy for this indication [6, 10–12].

MATERIALS AND METHODS

The present study was designed and conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [13].

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Data Sources and Search Strategy

We searched the PubMed and EMBASE databases as well as pertinent review articles and publicly available FDA records concerning the approval history of cefepime (http://www.access-data.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#aphist) to identify relevant studies. We also screened the references of all potentially eligible studies. The term (Cefepim* OR BMY-28142 OR Maxipime OR Maxcef OR Cepimax OR Cepimex OR Axepim) AND (tumor OR cancer OR carcinoma OR sarcoma OR neoplasia OR malignancy OR leukemia OR leukaemia OR lymphoma OR oncolog* OR hematolog* OR haematolog* OR neutropen*) was used. We imposed no restrictions on publication dates, and the date of last access was November 28, 2016. We only considered studies published in English, French, German, or Spanish. Three authors (N.A., M.E.F., A.A.), working independently, retrieved the search results and screened the titles and abstracts for potentially eligible studies. Any discrepancies were resolved by team consensus. In cases of missing data, an attempt was made to contact the study authors. Conference proceedings were not considered.

Study Selection

All randomized controlled trials reporting on the clinical efficacy of either (1) cefepime monotherapy versus alternative monotherapy or (2) cefepime plus aminoglycoside versus alternative monotherapy plus aminoglycoside (with the same aminoglycoside administered in both arms) in the setting of febrile neutropenia were eligible.

Outcomes of Interest, Data Extraction, and Quality Assessment

Data on clinical efficacy (primary outcome) were extracted and analyzed. Consistent with previous studies [7–9], clinical efficacy was defined as treatment success without therapy modification. If clinical efficacy was assessed at multiple time points, data from the time of last follow-up were included. In addition, similar to previous studies [7–9], in cases where clinical efficacy was reported both as a percentage of evaluable patients (per-protocol) and of the modified intent-to-treat population, the latter analysis was used to limit the impact of crossover and dropout bias. In trials that were retrieved from FDA records, the modified intent-to-treat analysis conducted by the FDA medical officers was used. Our outcomes also included overall mortality (death from any cause at the time of the last follow-up), infection-specific mortality, treatment modification, superinfections, adverse events, toxicity-related treatment discontinuation, treatment failure in clinically documented infections, and microbiologically documented infections. Data on all reported adverse events were included in our analysis, irrespective of their presumed etiology. If an outcome was reported on both a per-protocol basis and as a percentage of the modified intent-to-treat population, the latter analysis was used. Studies were classified by geographic region according to the definitions used by the World Health Organization

[14]. We assessed the effect of cefepime administration on primary and secondary outcomes and performed subgroup analyses according to predetermined study characteristics, which included analyses of the cefepime dose used, the comparator regimens used (cefepime vs carbapenems, cefepime vs cephalosporins, cefepime vs penicillins), and the study quality metrics. Moreover, trials assessing cefepime monotherapy versus alternative monotherapy were examined separately from trials investigating combination therapies.

Study quality was assessed with the methodological approach described by the Cochrane Collaboration [15]. Specifically, for each included study, 7 individual study characteristics (sequence generation, allocation concealment, blinding, outcome assessment, attrition bias, reporting bias, other bias) were rated as entailing a high, low, or unclear risk of bias. As such, each trial received 7 independent bias “ratings” and no cumulative indicator of study quality was calculated, in line with Cochrane recommendations [15].

Data Synthesis and Statistical Analysis

Given the minimal between-study heterogeneity ($I^2 < 30.0\%$), a fixed-effects meta-analysis was conducted to estimate the pooled risk ratio (RR) and 95% confidence intervals (CIs) for each outcome [7–9, 16]. An RR > 1 indicated a greater frequency of the respective outcome in the cefepime study arm. Publication bias was assessed with Egger’s test (ET) and between-study heterogeneity with I^2 [17, 18]. Data were excluded from our analysis if both treatment arms reported zero events for the examined outcome. Statistical analysis was performed with the STATA version 14 software package (StataCorp LP, College Station, TX), and statistical significance was defined as $P \leq .05$.

RESULTS

Review Process, Quality Assessment, and General Study Characteristics

The review process is presented in Figure 1. In brief, from the 2847 studies identified through our search, 30 trials fulfilled our inclusion criteria [11, 12, 19–46]. Furthermore, our screening of article references, review articles, and FDA records yielded 2 additional trials [47, 48], as well as supplementary data from a previously identified study [40]. Individual study characteristics are summarized in Table 1, and the studies that provided analyzable data for each outcome and the corresponding heterogeneity are presented in Table 2. All studies underwent quality evaluation (Supplemental Table 1 and Supplemental Table 2).

Clinical Efficacy, Treatment Modification, and Overall Mortality

Looking at clinical efficacy, cefepime treatment did not differ significantly compared with other antibiotics (RR = 0.990; 95% CI, 0.943–1.040; $P = .698$). This was the case in both the monotherapy and combination therapy subgroups (RR = 0.988; 95% CI, 0.934–1.045; $P = .675$ and RR = 0.996; 95% CI, 0.905–1.096; $P = .937$, respectively) (Figure 2). Egger’s test revealed no evidence of publication bias (ET = -0.480 ; $P = .636$) and

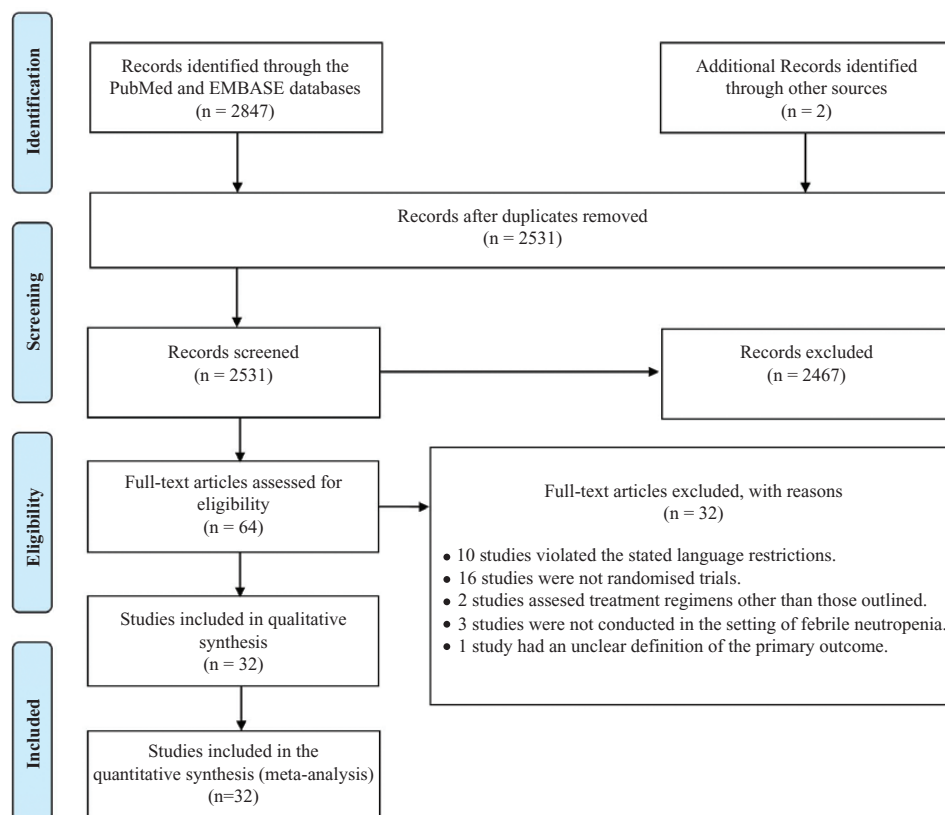


Figure 1. PRISMA flowchart: summary of the study review and selection process.

heterogeneity was minimal ($I^2 = 0.0\%$). Additional subgroup analyses also yielded nonsignificant findings, and the frequency of treatment modification was similar across study arms (Supplemental Results).

More importantly, cefepime was associated with increased overall mortality (RR = 1.321; 95% CI, 1.035–1.686; $P = .025$) (Figure 3). This was the case in the monotherapy subgroup (RR = 1.520; 95% CI, 1.138–2.031; $P = .005$) but not in the aminoglycoside combination therapy subgroup (RR = 0.927; 95% CI, 0.584–1.473; $P = .749$). It is interesting to note that cefepime dosage appeared to impact mortality, because trials that used low-dose monotherapy demonstrated increased mortality in the cefepime arm (RR = 1.682; 95% CI, 1.038–2.727; $P = .035$), a result that was based on 6 studies (1225 patients) [11, 12, 20, 30, 35, 41]. Of note is that only 1 of the aforementioned studies was conducted among pediatric patients [41], and its exclusion did not affect the results (RR = 1.784; 95% CI, 1.088–2.924; $P = .022$).

On the contrary, trials that used high-dose (2 grams/8 hours, 50 mg/kg per 8 hours) regimens were not associated with increased mortality in the cefepime arm (RR = 1.387; 95% CI, 0.958–2.008; $P = .083$ and RR = 1.425; 95% CI, 0.979–2.075; $P = .064$ for all trials and monotherapy, respectively; 10 trials, 1720 patients) [19, 21–23, 28, 34, 40, 45, 47, 48]. It is notable that only 1 study [28] examined combination therapy, whereas

the rest were monotherapy trials. The inclusion of previously unpublished data, that were reported for the first time by the Cochrane [9] and FDA [3] studies enabled us to incorporate 4 additional high-dose monotherapy trials [24, 36, 39, 46] into the mortality analysis, for a final population of 2293 patients. More importantly, our findings remained unaffected by the inclusion of these unpublished data (RR = 1.337; 95% CI, 0.962–1.859; $P = .084$ or RR = 1.365; 95% CI, 0.978–1.905; $P = .068$ for all trials and monotherapy, respectively [Cochrane data [9]] and RR = 1.313; 95% CI, 0.948–1.818; $P = .101$ or RR = 1.339; 95% CI, 0.964–1.861; $P = .082$ for all trials and monotherapy, respectively [FDA data [3]]). It is notable that 4 of these studies provided data on pediatric patients [19, 34, 36, 45], and, after excluding pediatric studies from the analysis, the association between high-dose cefepime administration and overall mortality remained nonsignificant (RR = 1.373; 95% CI, 0.973–1.938; $P = .072$ and RR = 1.405; 95% CI, 0.991–1.992; $P = .056$ for all trials and monotherapy, respectively). Furthermore, 3 trials that used varying cefepime doses (50 mg/kg every 8–12 hours, 1–2 grams/8 hours, and 1–2 grams/12 hours, respectively [25, 31, 44]) were excluded, because we were unable to ascertain how many patients received high versus low doses.

Furthermore, cefepime monotherapy was associated with increased overall mortality, compared with carbapenem

Table 1. Study Characteristics

| Study | Publication Year | Patients | Episodes | Monotherapy | Regimen | FEP Dose | Region |
|-------------------|------------------|----------|----------|-------------|-----------------------------------|--------------------|-----------------------|
| Aamir [19] | 2016 | 40 | 40 | Yes | FEP vs TZP | 50 mg/kg per 8h | Other (India) |
| Aoun [47] | n/a | 111 | 128 | Yes | FEP vs CAZ | 2g/8h | Europe |
| Biron [20] | 1998 | 380 | 400 | Yes | FEP vs IPM | 2g/12h | Europe |
| Bohme [21] | 1998 | 88 | 102 | Yes | FEP vs TZP | 2g/8h | Europe |
| Bow [22] | 2006 | 528 | 528 | Yes | FEP vs TZP | 2g/8h | Multiple ^a |
| Chandrasekar [23] | 2000 | 276 | 276 | Yes | FEP vs CAZ | 2g/8h | Americas |
| Cherif [24] | 2004 | 180 | 207 | Yes | FEP vs IPM | 2g/8h | Europe |
| Chuang [25] | 2002 | 95 | 120 | Yes | FEP vs CAZ | 50 mg/kg per 8-12h | Western Pacific |
| Corapcioglu [26] | 2006 | 27 | 50 | Yes | FEP vs TZP | 50 mg/kg per 8h | Europe |
| Cordonnier [27] | 1997 | 353 | 353 | No | (FEP+AMK) vs (CAZ+AMK) | 2g/12h | Europe |
| Cornely [28] | 2001 | 207 | 207 | No | (FEP+GEN) vs (CRO+GEN) | 2g/8h | Europe |
| Erman [29] | 2001 | 208 | 208 | No | (FEP+AMK) vs (CAZ+AMK) | 2g/12h | Europe |
| Fujita [30] | 2016 | 45 | 45 | Yes | FEP vs MEM | 2g/12h | Western Pacific |
| Ghalaut [31] | 2007 | 40 | 40 | Yes | FEP vs CAZ | 1-2g/8h | Other (India) |
| Glauser [48] | n/a | 281 | 324 | Yes | FEP vs CAZ | 2g/8h | Europe |
| Gomez [32] | 2010 | 190 | 317 | No | (FEP+AMK) vs (TZP+AMK) | 2g/12h | Europe |
| Kebudi [33] | 2001 | 33 | 63 | Yes | FEP vs CAZ | 50 mg/kg per 8h | Europe |
| Kutluk [34] | 2004 | 30 | 49 | Yes | FEP vs MEM | 50 mg/kg per 8h | Europe |
| Kwon [35] | 2008 | 116 | 116 | Yes | FEP vs PAPM | 2g/12h | Western Pacific |
| Mustafa [36] | 2001 | 104 | 104 | Yes | FEP vs CAZ | 50 mg/kg per 8h | Americas |
| Nakagawa [12] | 2013 | 255 | 255 | Yes | FEP vs PAPM/MEM | 2g/12h | Western Pacific |
| Nakane [11] | 2015 | 376 | 376 | Yes | FEP vs CZOP, MEM/IMP | 2g/12h | Western Pacific |
| Naseem [37] | 2011 | 107 | 201 | Yes | FEP vs TIM | 2g/8h | Other (Pakistan) |
| Oguz [38] | 2006 | 37 | 65 | Yes | FEP vs MEM | 50 mg/kg per 8h | Europe |
| Raad [39] | 2003 | 251 | 251 | Yes | FEP vs MEM | 2g/8h | Americas |
| Ramphal [40] | 1996 | 90 | 104 | Yes | FEP vs CAZ | 2g/8h | Americas |
| Sano [41] | 2015 | 53 | 213 | Yes | FEP vs TZP | 100mg/kg per day | Western Pacific |
| Sanz [42] | 2002 | 969 | 984 | No | (FEP+AMK) vs (TZP+AMK) | 2g/8h | Europe |
| Sarashina [43] | 2014 | 64 | 223 | Yes | FEP vs CZOP | 100mg/kg per day | Western Pacific |
| Tamura [44] | 2002 | 83 | 83 | Yes | FEP vs carbapenems (PAPM/IMP/MEM) | 1-2g/12h | Western Pacific |
| Uygun [45] | 2009 | 69 | 127 | Yes | FEP vs TZP | 50 mg/kg per 8h | Europe |
| Wang [46] | 1999 | 38 | 45 | Yes | FEP vs CAZ | 2g/8h | Western Pacific |

Abbreviations: AMK, amikacin; CAZ, ceftazidime; CRO, ceftriaxone; CZOP, ceftiozan; FEP, cefepime; GEN, gentamicin; IMP, imipenem/cilastatin; MEM, meropenem; n/a, not applicable; PAPM, panipenem; TIM, ticarcillin/clavulanate; TZP, piperacillin/tazobactam.

^aThe trial included patients from the United States, Canada, and Australia.

monotherapy (RR = 1.950; 95% CI, 1.177–3.228; $P = .009$), a result that was based on 6 studies (1202 patients) [11, 12, 20, 30, 34, 35]. However, 5 of the studies used low-dose cefepime regimens [11, 12, 20, 30, 35], indicating that this association may stem from the use of low-dose regimens and not from inferiority compared with carbapenems. After including unpublished mortality data from 2 earlier meta-analyses [3, 9], the comparison of cefepime versus carbapenems expanded to a total of 9 studies [11, 12, 20, 24, 30, 34, 35, 39, 44], and 5 of these studies [11, 12, 20, 30, 35] used low-dose regimens. More importantly, cefepime monotherapy was again associated with increased overall mortality (RR = 1.690; 95% CI, 1.110–2.572; $P = .014$ and RR = 1.668; 95% CI, 1.089–2.555; $P = .019$, after including data from the Cochrane [9] and FDA [3] meta-analyses, respectively). It is notable that no difference in overall mortality was noted after comparing cefepime with noncarbapenem antibiotics (RR = 1.169; 95% CI, 0.888–1.541; $P = .266$).

Study quality ratings were also shown to impact outcomes, and studies with a low risk of bias in sequence generation (the method by which randomization was performed) supported a positive association between cefepime administration and overall mortality (RR = 1.533; 95% CI, 1.135–2.070; $P = .005$). This was also the case among studies with a low risk of bias in outcome assessment (the process through which treatment efficacy was determined) and allocation concealment (the method by which treatment allocation was concealed) (RR = 1.655; 95% CI, 1.047–2.616; $P = .031$ and RR = 1.798; 95% CI, 1.291–2.504; $P = .001$, respectively). Furthermore, studies with a low risk of other bias also demonstrated increased mortality in the cefepime arm (RR = 1.468; 95% CI, 1.066–2.021; $P = .019$). In contrast, the pooled results of studies that displayed a high or unclear risk of bias in the study areas detailed in the Methods section did not support the association between cefepime administration and overall mortality (the detailed quality assessment of all trials

Table 2. Number of Studies Providing Data for Each Included Outcome and Corresponding Between-Study Heterogeneity

| Outcome | Studies Reporting on Outcome | I^2 |
|---|---|-------|
| Clinical efficacy | 32 [11, 12, 19–48] | 0.0% |
| Overall mortality (main analysis) | 21 [11, 12, 19–23, 25, 27–32, 34, 35, 40, 41, 45, 47, 48] | 0.0% |
| Overall mortality (low-dose cefepime monotherapy vs alternative monotherapy) | 6 [11, 12, 20, 30, 35, 41] | 0.0% |
| Overall mortality (cefepime vs carbapenems) | 6 [11, 12, 20, 30, 34, 35] | 0.0% |
| Overall mortality (main analysis/Cochrane, unpublished data) | 26 [11, 12, 19–25, 27–32, 34–36, 39–41, 44–48] | 0.0% |
| Overall mortality (low-dose cefepime monotherapy vs alternative monotherapy/Cochrane, unpublished data) | 6 [11, 12, 20, 30, 35, 41] | 0.0% |
| Overall mortality (cefepime vs carbapenems/Cochrane, unpublished data) | 9 [11, 12, 20, 24, 30, 34, 35, 39, 44] | 0.0% |
| Overall mortality (main analysis/US Food and Drug Administration [FDA], unpublished data) | 26 [11, 12, 19–25, 27–32, 34–36, 39–41, 44–48] | 0.0% |
| Overall mortality (low-dose cefepime monotherapy vs alternative monotherapy/FDA, unpublished data) | 6 [11, 12, 20, 30, 35, 41] | 0.0% |
| Overall mortality (cefepime vs carbapenems/FDA, unpublished data) | 9 [11, 12, 20, 24, 30, 34, 35, 39, 44] | 0.0% |
| Infection-specific mortality | 18 [20, 22–25, 27, 28, 30, 32, 34, 35, 37, 40–42, 45, 46, 48] | 0.0% |
| Treatment modification | 21 [12, 20–27, 29, 32–34, 36–38, 40, 42, 45, 46, 48] | 0.0% |
| Superinfection | 12 [23, 25, 27, 29, 32, 36, 39, 41–43, 46, 48] | 0.0% |
| Treatment failure in clinically documented infections | 16 [12, 20–22, 24, 25, 27, 28, 32, 35–39, 42, 46] | 0.0% |
| Treatment failure in microbiologically documented infections | 23 [12, 20–25, 27, 28, 32, 35–43, 45–48] | 0.0% |
| Adverse events | 24 [11, 12, 19–22, 24–30, 32, 35–37, 39, 40, 42, 44, 46–48] | 21.5% |
| Adverse events (low-dose cefepime monotherapy vs alternative monotherapy) | 5 [11, 12, 20, 30, 35] | 27.2% |
| Adverse events (cefepime vs carbapenems) | 8 [11, 12, 20, 24, 30, 35, 39, 44] | 0.0% |
| Discontinuation due to adverse events | 15 [11, 20–25, 27–29, 32, 36, 40, 47, 48] | 0.0% |
| Discontinuation due to adverse events (high-dose cefepime monotherapy vs alternative monotherapy) | 8 [21–24, 36, 40, 47, 48] | 0.0% |

can be viewed in Supplemental Tables 1 and 2, and the results of the performed subanalyses according to study quality are presented in Supplemental Table 3).

Treatment Failure in Patients With Clinically and Microbiologically Documented Infections, Infection-Specific Mortality, and Superinfections

Treatment failure among patients with clinically documented infections was significantly more common with cefepime therapy (RR = 1.143; 95% CI, 1.004–1.300; $P = .043$) (16 trials, reporting on 355 cefepime-treated infections vs 384 infections

treated with other antibiotics [12, 20–22, 24, 25, 27, 28, 32, 35–39, 42, 46]). However, additional subanalyses yielded non-significant findings (Supplemental Results). It is interesting to note that the incidence of treatment failure in microbiologically documented infections (23 trials, reporting on 455 cefepime-treated infections vs 420 infections treated with other antibiotics [12, 20–25, 27, 28, 32, 35–43, 45–48]) was similar across study arms (Supplemental Results). Furthermore, the occurrence of superinfections (12 trials, reporting on 174 vs 161 superinfections in the cefepime and comparator study arms, respectively [23, 25, 27, 29, 32, 36, 39, 41–43, 46, 48]) was not significantly different in the cefepime arm (Supplemental Results). Finally, infection-specific mortality (18 trials, 4007 patients [20, 22–25, 27, 28, 30, 32, 34, 35, 37, 40–42, 45, 46, 48]) was similar in patients treated with cefepime or other antibiotics (Supplemental Results).

Incidence of Adverse Events and Toxicity-Related Treatment Discontinuation

Next, we investigated whether toxicity was also related to cefepime dose. Indeed, we found that the overall frequency of adverse events was similar among patients treated with cefepime or other antibiotics (RR = 0.964; 95% CI, 0.906–1.026; $P = .246$ and RR = 0.953; 95% CI, 0.899–1.011; $P = .112$ for all studies and cefepime monotherapy, respectively) but significantly lower among patients treated with low-dose cefepime monotherapy (RR = 0.681; 95% CI, 0.510–0.910; $P = .009$). In contrast, in trials using high-dose cefepime monotherapy, the frequency of adverse events was similar in both study arms (RR = 0.998; 95% CI, 0.945–1.054; $P = .946$). Toxicity-related treatment discontinuation was more frequent among patients treated with cefepime monotherapy (RR = 1.566; 95% CI, 1.094–2.241; $P = .014$). More importantly, cefepime dosing impacted the likelihood of treatment discontinuation. Specifically, a statistically significant increase in treatment discontinuation was noted among patients receiving a high-dose regimen (RR = 1.535; 95% CI, 1.047–2.249; $P = .028$ and RR = 1.558; 95% CI, 1.055–2.302; $P = .026$ for all studies and monotherapy, respectively) but not among patients receiving a low-dose regimen (RR = 0.913; 95% CI, 0.525–1.587; $P = .746$ and RR = 1.494; 95% CI, 0.579–3.856; $P = .407$ for all studies and monotherapy, respectively). Additional information on the adverse events that led to treatment discontinuation is provided in Supplemental Results.

DISCUSSION

Much controversy has surrounded the use of cefepime for febrile neutropenia [3, 9], yet no satisfactory interpretation of the reported association of cefepime with increased mortality has been provided to date [7–9]. Moreover, even though the FDA recommends a dose of 2 grams/8 hours or 50 mg/kg per 8 hours for this indication [3, 49], lower doses are used in practice with considerable frequency [3, 6, 10]. In this context, the present

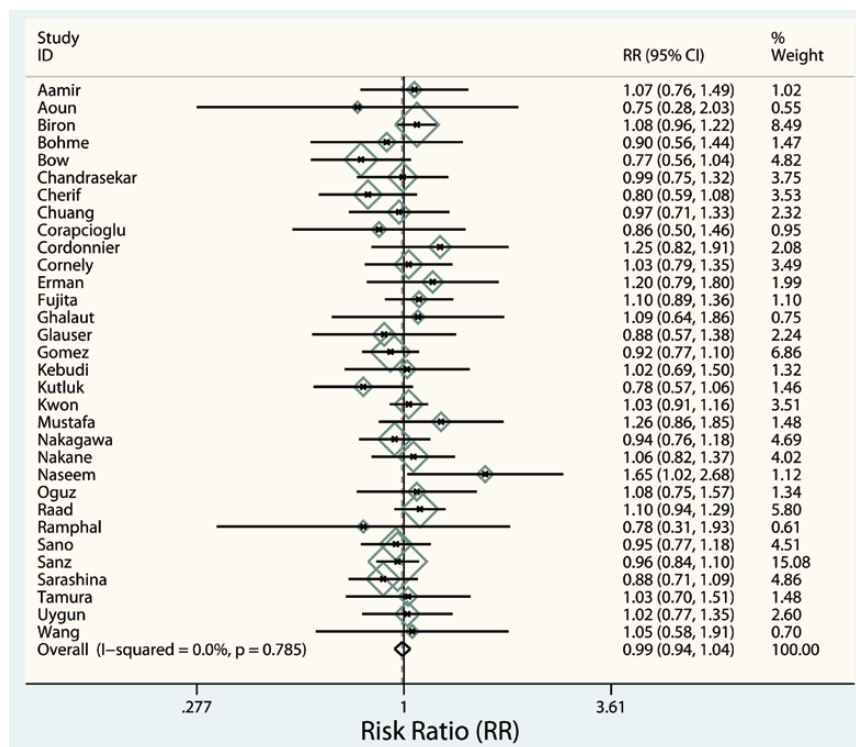


Figure 2. Forest plot of included studies. Relative risk (RR) estimates of the clinical efficacy of cefepime versus comparator regimens. Abbreviation: CI, confidence interval.

study aimed to reassess the safety and efficacy of cefepime for this indication, and we detected increased overall mortality and reduced treatment efficacy in clinically documented infections in the cefepime arm and increased toxicity associated with high-dose regimens. More importantly, cefepime dosage appears to have a previously underappreciated impact on outcomes, because trials that used low-dose cefepime monotherapy demonstrated significantly increased overall mortality in the cefepime arm, unlike studies that used high-dose cefepime regimens. It is interesting to note that increased toxicity was observed with high-dose cefepime regimens.

In line with previous studies, cefepime was associated with increased mortality [7–9]. The validity of this finding is supported by the fact that the association was more pronounced among studies with a lower risk of bias in study design and by the inferior efficacy of cefepime in clinically documented infections. In light of these results, it might seem paradoxical that cefepime demonstrated similar clinical efficacy with other antibiotics. However, clinical efficacy is a less reliable measure of treatment effectiveness than mortality, because definitions of treatment success vary across studies, and treatment modification may stem from considerations other than treatment failure. As such, consistent with previous reports [7–9], the overall clinical efficacy of cefepime was similar to that of alternative regimens.

The impact of cefepime dosing on mortality is particularly important, because the advantages and disadvantages of

high-dose versus low-dose regimens have not been studied thoroughly. Specifically, although the FDA recommends the use of high-dose regimens [49], some reports advocate the use of lower doses, despite the lack of conclusive evidence of therapeutic equivalence [6, 10]. Low-dose cefepime regimens have a lower probability of achieving the target serum concentrations necessary for eradicating resistant pathogens, such as *Pseudomonas aeruginosa* [50–52], and may, consequently, display reduced in vivo efficacy. However, it should be noted that our analysis is inadequately powered to conclusively prove the inferiority of low-dose compared with high-dose cefepime regimens. Specifically, the 95% CIs of the low-dose cefepime versus comparators and high-dose cefepime versus comparators subanalyses overlap. As such, the noninferiority of low-dose regimens compared with high-dose regimens cannot be conclusively rejected by the present analysis. Nevertheless, the disproportionate impact of a small number of low-dose trials on mortality and the existence of pharmacokinetic data that question the efficacy of low-dose cefepime regimens strongly support the need to formally assess the equivalence of different dosing recommendations.

It is interesting to note that cefepime-related toxicity was also shown to be dose dependent. In particular, a significantly increased rate of toxicity-related treatment discontinuation was noted in the cefepime arm, an effect driven by trials that used high-dose regimens. This was not the case with low-dose cefepime monotherapy, which was associated with significantly

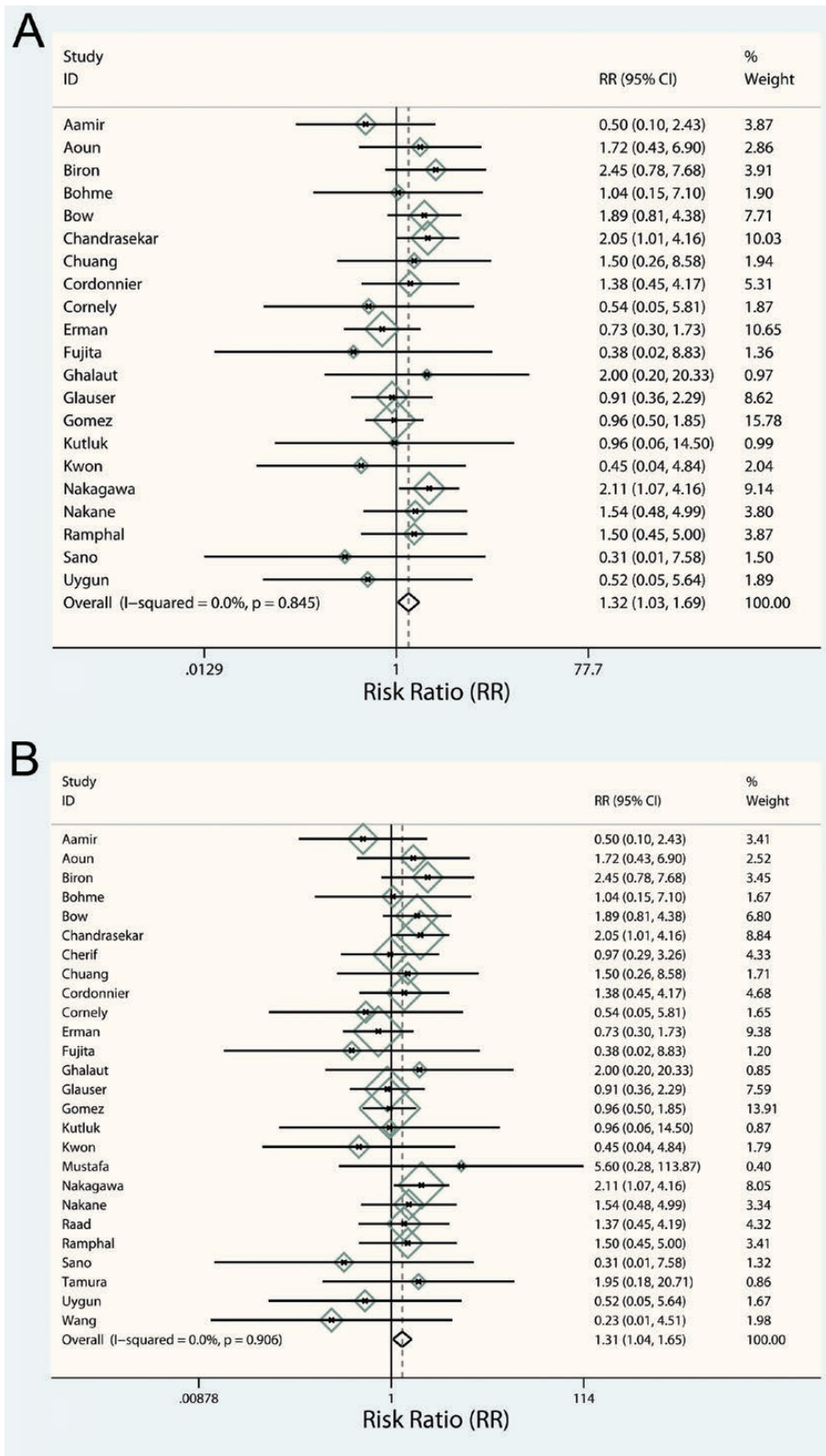


Figure 3. Forest plot of included studies. Relative risk (RR) estimates of the overall mortality in the cefepime study arm versus comparator regimens according to our original analysis (A). Additional pooled analyses including supplementary unpublished data reported by the Cochrane meta-analysis (B) and the US Food and Drug Administration meta-analysis (C) are also depicted. Abbreviation: CI, confidence interval.

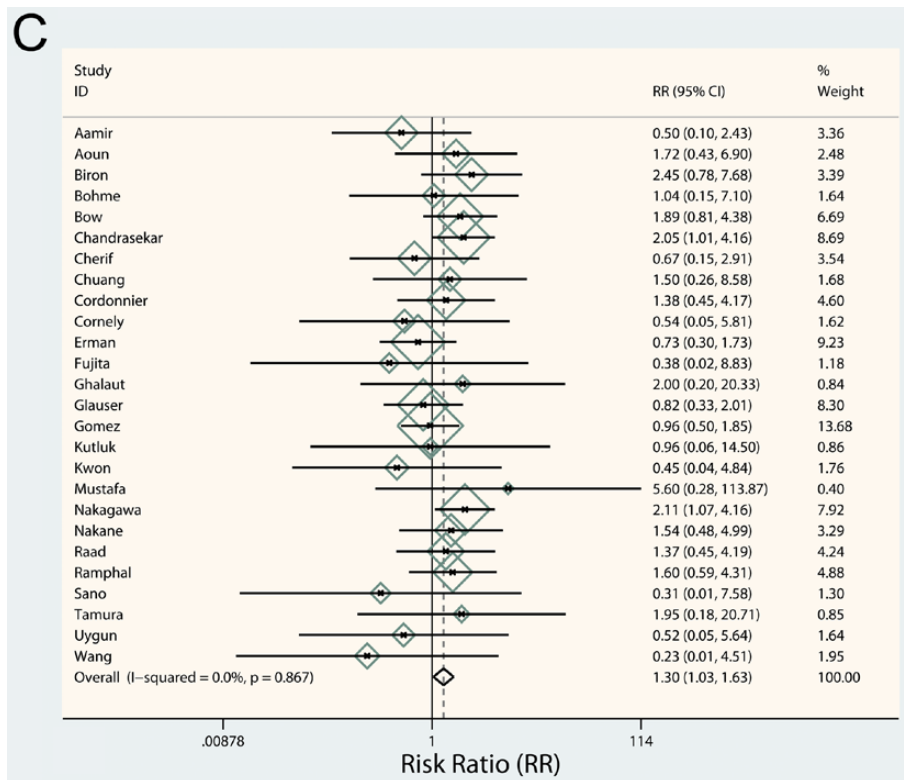


Figure 3. Continued.

fewer adverse events and similar rates of treatment discontinuation, compared with alternative monotherapy. In turn, it is possible that an increased rate of toxicity-related treatment discontinuation may impact outcomes either directly, by causing a “break” in effective antimicrobial coverage during treatment modification, or indirectly, by serving as a proxy for an increased rate of severe toxicity in the cefepime arm, as has been previously hypothesized [8]. Taken together, these findings suggest that higher doses may result in enhanced efficacy but at the cost of increased toxicity. In turn, increased toxicity may help to explain why a nonsignificant trend towards increased mortality was sometimes observed in the cefepime arm, even in studies that used high-dose regimens. Although it is difficult to quantify the relative impact of toxicity and efficacy on outcomes, it is important to note that high-dose regimens may also have inherent limitations. As a result, longitudinal monitoring of adverse events will prove essential to better characterizing the toxicity profile of cefepime.

Although a pattern of dose-dependent efficacy may, by and large, explain the association of cefepime with increased mortality, possible inferiority compared with carbapenem therapy may also contribute to these findings. As detailed above, cefepime was associated with increased overall mortality in comparison with carbapenem-based regimens, and no similar association was detected when comparing cefepime with other antibiotics, thus suggesting that cefepime may be specifically

inferior to carbapenem therapy. Previous meta-analyses failed to detect significant differences in mortality after comparing cefepime with other antibiotics, including carbapenems [7–9]. In turn, this may be explained by changing antibiotic resistance patterns over time. Specifically, carbapenems are known to be more efficacious than other β -lactams in the treatment of extended spectrum β -lactamase (ESBL)-producing pathogens [53], and 2 newly published trials which demonstrated increased mortality in cefepime-treated versus carbapenem-treated patients were conducted in Japan [11, 12], where an increase in ESBL prevalence has been reported [54–56]. However, it should be noted that the majority of trials comparing cefepime with carbapenem therapy also used low-dose cefepime regimens [11, 12, 20, 30, 35], and, consequently, cefepime dosing may have confounded this association, or low-dose cefepime monotherapy may be at a particular disadvantage, compared with carbapenems.

Regarding study limitations, the present meta-analysis is restricted by the quality and quantity of the data provided by the included studies. For example, information on secondary outcomes was occasionally missing from the published studies, thus increasing the likelihood of a type II error in the respective analyses. Unpublished mortality data provided by the FDA [3] and Cochrane [9] studies were used in an attempt to mitigate this limitation. Furthermore, we decided not to include unpublished conference proceedings in the present study, because conference

proceedings rarely report details on trial methodology, which are necessary to evaluate study quality. To assess whether this decision influenced our results, we performed a subanalysis that incorporated data from unpublished conference proceedings, reported in the most recent Cochrane review [9], and our results were unaffected (Supplemental Results). In addition, although the present meta-analysis incorporated more studies than previous reports, it should be noted that many factors (study quality, patient characteristics, etc) could confound our results, and our capacity to adjust for them while maintaining adequate statistical power is extremely limited, particularly in subanalyses with a small number of included studies. Furthermore, low statistical power complicates the interpretation of subgroup analyses with respect to the impact of cefepime dosing on outcomes. Specifically, despite the significant association of cefepime with mortality in trials that used low-dose regimens, and the lack of such an association among trials using high-dose regimens, the corresponding 95% CIs overlap. The latter finding probably stems from the reduction in statistical power that accompanies division of the patient population into subgroups. In turn, an accurate assessment of the relative efficacy of high-dose versus low-dose cefepime regimens is difficult to perform.

CONCLUSIONS

In conclusion, the present meta-analysis not only confirmed the association of cefepime therapy with increased overall mortality among patients with febrile neutropenia, but it also identified potential underlying associations. More specifically, cefepime dosage may exert an important impact on outcomes, because low-dose cefepime monotherapy was associated with decreased toxicity, at the expense of increased overall mortality. Possible inferiority compared with carbapenems, reduced efficacy in clinically documented infections, and higher rates of toxicity-related treatment discontinuation may also contribute to this association. More importantly, our results suggest that increased mortality may be limited to specific treatment settings and dosing regimens. Although our findings require confirmation by future trials, the present study suggests that outcomes may be optimized by adjusting cefepime dosing recommendations and treatment indications, rather than by discontinuing the use of this important antibiotic.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. N. A. conceptualized and designed the study, participated in data collection, extraction, and interpretation, performed the statistical analysis, prepared tables and figures, wrote and drafted the initial manuscript, and approved the final manuscript as submitted. M. E.

F. conceptualized and designed the study, participated in data collection, extraction, and interpretation, performed the statistical analysis, prepared tables and figures, wrote and drafted the initial manuscript, and approved the final manuscript as submitted. A. A. designed the study, participated in data collection, extraction, and interpretation, wrote and drafted the initial manuscript, and approved the final manuscript as submitted. M. A. designed the study, participated in data interpretation, drafted the initial manuscript, and approved the final manuscript as submitted. E. M. conceptualized and designed the study, participated in data interpretation, reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

N. A., M. E. F., and E. M. accept full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish. N. A. and M. E. F. take responsibility for the integrity of the data and the accuracy of the data analysis

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