MAJOR ARTICLE

# Meta-Analysis of a Possible Signal of Increased Mortality Associated with Cefepime Use

**Peter W. Kim,[1] Yu-te Wu,[2] Charles Cooper,[2] George Rochester,[2] Thamban Valappil,[2] Yan Wang,[2] Cynthia Kornegay,[3] and Sumathi Nambiar[1]**

[1]Office of Antimicrobial Products, [2]Office of Biostatistics, and [3]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland

**(See the editorial commentary by Freifeld and Sepkowitz, on pages 390–391.)**

***Background.*** On the basis of meta-analyses, concern has been raised regarding a possible signal of increased mortality associated with the use of cefepime versus other β-lactam antibiotics. To further investigate this possible signal, we accessed findings and data from published and unpublished cefepime clinical trials.

***Methods.*** We performed meta-analyses using trial- and patient-level data from comparative trials. Trial-level analyses were performed using summary data from all patients in the trials, and patient-level analyses were performed on trials for which patient-level data were available. Thirty-day, all-cause mortality was analyzed using the Mantel-Haenszel adjusted risk difference (ARD) method.

***Results.*** The trial-level meta-analysis was based on 88 trials (9467 cefepime patients and 8288 comparator patients). The 30-day, all-cause mortality rates were 6.21% (588/9467) for the cefepime patients and 6.00% (497/8288) for comparator patients (ARD per 1000 population, 5.38; 95% confidence interval [CI], −1.53 to 12.28). In the patient-level analysis (35 trials, 5058 cefepime patients, and 3976 comparator patients), 30-day, all-cause mortality rates were 5.63% (285/5058) for cefepime patients and 5.68% (226/3976) for comparator patients (ARD per 1000 population, 4.83; 95% CI, −4.72 to 14.38). A sensitivity analysis based solely on the 24 febrile neutropenia trials did not show a statistically significant increase in mortality with cefepime use (ARD per 1000 population, 9.67; 95% CI, −2.87 to 22.21).

***Conclusions.*** In both trial-level and patient-level meta-analyses, we did not identify a statistically significant increase in mortality among cefepime-treated patients, compared with those treated with other antibacterials.

Cefepime was approved by the US Food and Drug Administration (FDA) in 1996 for the following indications: pneumonia (moderate to severe), uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and complicated intra-abdominal infections. In 1997, cefepime was approved by the FDA as monotherapy for the empiric treatment of febrile neutropenia and is the only antibacterial agent approved as monotherapy for this indication in the United States. Cefepime is included as a recommended therapy in treatment guidelines for febrile neutropenia [1].

An increased risk of mortality associated with cefepime use has been reported in 2 previously published meta-analyses. Paul et al [2] published a trial-level meta-analysis in 2006 based on 17 publications reporting increased 30-day mortality with cefepime relative to other β-lactams when used for empiric antibacterial monotherapy for febrile neutropenia (risk ratio [RR], 1.44; 95% confidence interval [CI], 1.06–1.94). In 2007, the same group (Yahav et al [3]) published a trial-level meta-analysis based on 57 publications that showed increased 30-day mortality associated with cefepime, compared with other β-lactams (RR, 1.26; 95% CI, 1.08–1.49), for the following clinical conditions combined: febrile neutropenia, pneumonia, urinary tract or gynecologic infections, and other or mixed infections [3]. This finding was based on mortality data from 41 of the 57

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Reprints or correspondence: Dr Peter W. Kim, Office of Antimicrobial Products, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993 (peter.kim@fda.hhs.gov).

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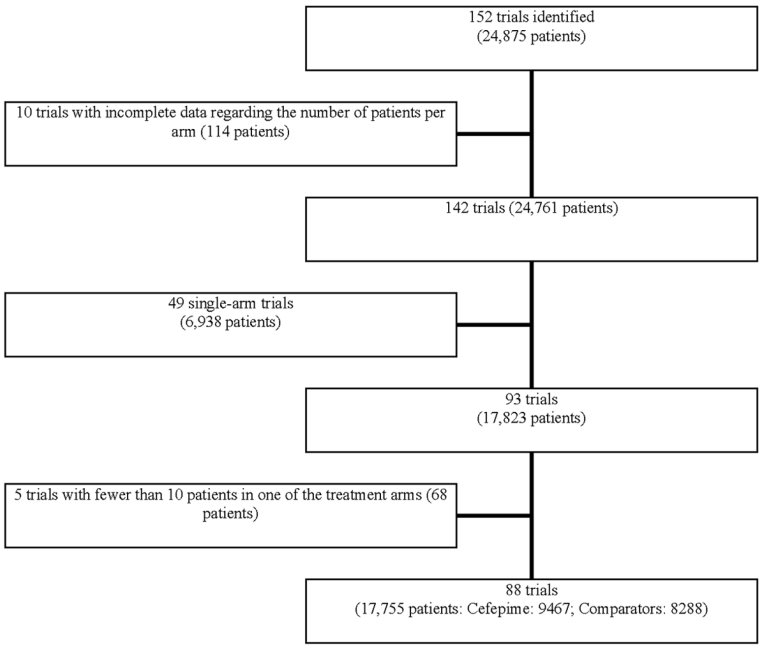


**Figure 1.** Flow diagram for the selection of trials in the trial-level analysis.

publications, because mortality data were missing from 16 publications; higher mortality rates were also noted in the subset of 19 febrile neutropenia publications (RR, 1.42; 95% CI, 1.09–1.84). The 2007 meta-analysis included 15 of the 17 cefepime publications from the 2006 meta-analysis; 2 publications were excluded because the trials were quasi-randomized.

Because of concern regarding the possible increased risk of mortality associated with cefepime use, we conducted a meta-analysis accessing both published and unpublished cefepime clinical trial data and findings. Our primary objective was to examine whether cefepime use was associated with an increased risk of mortality relative to the comparator drugs in randomized controlled trials. Our secondary objective was to examine whether the risk of mortality was associated with covariates such as clinical condition treated, comparator drug(s), and demographic and baseline risk factors (eg, presence of a microbiologically documented pathogen, baseline pathogen susceptibility, presence of renal failure, active malignant neoplasm, and bone marrow transplant). To gain a better understanding of the causes of death, including the possibility of lack of drug efficacy, we reviewed the case report forms (CRFs) of all patients who died in the febrile neutropenia trials that had previously been submitted to the FDA for registration purposes.

## METHODS

We attempted to develop a complete list of all clinical trials of cefepime encompassing all published and unpublished trials, including those not previously submitted to the FDA. We also attempted to obtain mortality data that were missing from 16 of the 57 publications included in the 2007 meta-analysis described herein [4–19]. Information gleaned from this process was used to define the set of trials included in our meta-analyses.

Both patient- and trial-level data were sought from the pharmaceutical sponsor and from the authors of the publications. Trial-level data included information by trial regarding number of patients, number of deaths, clinical condition treated, and comparator drug(s) used. In addition, the patient-level data included variables for patient and trial identification, age, sex, race, study location, and any of the following present at baseline: any pathogen recovered, all isolated pathogens susceptible to study therapy, presence of a fungal pathogen, whether an infection was monomicrobial or polymicrobial, presence of renal insufficiency or failure, active malignant neoplasm, and history of bone marrow transplantation.

Trials were characterized on the basis of level of data (patient vs trial), whether mortality data were based on the intent-to-treat (preferred due to randomization protection) or the clinically evaluable subset population, whether mortality rates were based on actual patients versus episodes of therapy (febrile neutropenia trials only), phase of trials, clinical condition treated, comparator agent(s) used, combination regimen used (if applicable), use of blinding, duration of follow-up, and inclusion in the 2007 meta-analysis.

A statistical analysis plan was developed before performing the meta-analysis. In our meta-analysis, we included the following: (1) all parallel-arm, randomized, active-controlled trials con-

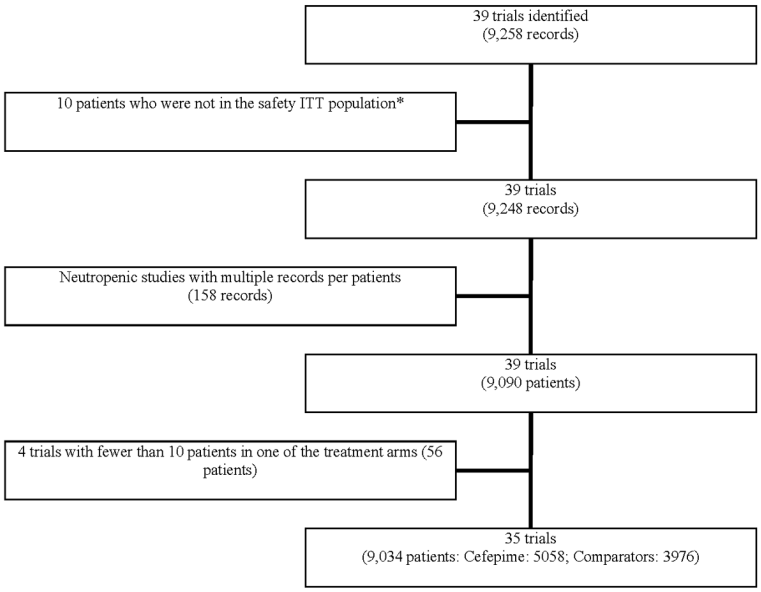


**Figure 2.** Flow diagram for the selection of trials in the patient-level analysis. *In the patient-level analysis, the safety intent-to-treat (ITT) population was defined as all patients who received at least 1 dose of study drug and whose 30-day, all-cause mortality status was known.

ducted with cefepime with or without adjunct therapy; (2) all US and non-US trials, including those not previously submitted to the FDA; and (3) trials with at least 10 patients per treatment arm. Figures 1 and 2 outline the process used to select trials included in the trial- and patient-level meta-analyses.

To include trials with no deaths in both treatment arms, meta-analysis was performed using the Mantel-Haenszel adjusted risk difference (ARD) method (Comprehensive Meta Analysis, version 2.2; BioStat), which uses a weighted average based on each trial's size and magnitude of point estimate [20]. The ARD and 95% CIs were calculated using a fixed-effects model. The primary endpoint was all-cause mortality 30-days after therapy. Several sensitivity analyses (eg, exact method for odds ratio and Cox proportional hazards model stratified by trial) were conducted to check the robustness of the findings [21]. A sensitivity analysis using a random-effects model was also performed.

The 7 comparative febrile neutropenia trials with patient-level data were reviewed in further detail to evaluate the cause(s) of death. This included the review of all CRFs from patients who died in the febrile neutropenia trials and analyses based on available clinical trial data. From these sources, we attempted to identify the most likely cause(s) of death for each patient and potential contributing factors (comorbidities, adverse events, and documented pathogens). Adverse events of special interest were identified and reviewed, including those associated with death, such as neurologic impairment or seizure, renal toxic effects, liver toxic effects, study drug failure, and central nervous system hemorrhage.

## RESULTS

***Trial-level analysis.*** Eighty-eight randomized, comparative trials, comprising 9467 cefepime-treated patients and 8288 comparator patients, were included in the trial-level analysis. Table 1 gives the number of trials and patients in each of the treatment groups by clinical condition treated. The febrile neutropenia and pneumonia trials comprised 30.7% and 22.80% of the total trial-level study population, respectively. Overall, 588 (6.21%) of 9467 cefepime-treated patients died within 30 days, compared with 497 (6.00%) of 8288 comparator patients. Meta-analysis based on these 88 trials showed no significant difference in mortality between cefepime-treated and comparator patients with an ARD per 1000 population of 5.38 (95%

**Table 1. Trials by Clinical Condition Treated in the Trial-Level Data**

| Clinical condition | No. of trials | No. (%) of patients | |
|---|---|---|---|
| | | Cefepime | Comparator |
| Febrile neutropenia | 24 | 2791 (29.48) | 2658 (32.07) |
| Intra-abdominal infection | 7 | 628 (6.63) | 470 (5.67) |
| Pneumonia | 26 | 2228 (23.53) | 1821 (21.97) |
| Urinary tract infection | 7 | 763 (8.06) | 490 (5.91) |
| Skin structure infection[a] | 2 | 335 (3.54) | 165 (1.99) |
| Other | 22 | 2722 (28.75) | 2684 (32.38) |
| Total | 88 | 9467 (100) | 8288 (100) |

[a] Not differentiated by uncomplicated versus complicated skin and skin structure infections.

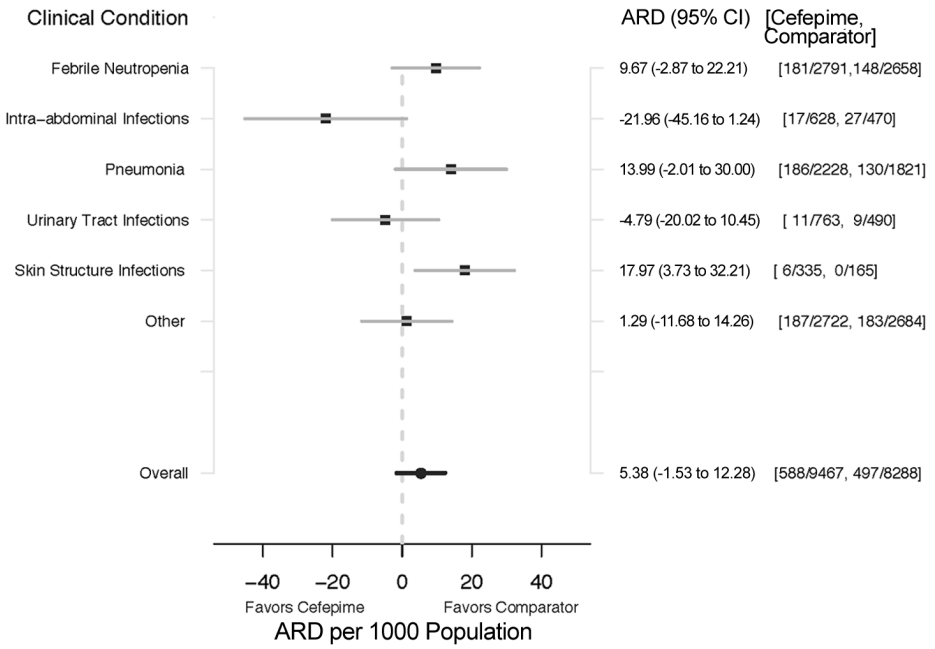


**Figure 3.** Trial-level meta-analysis (fixed-effects model) of randomized controlled trials of cefepime versus comparator in the overall population and in subgroups by the clinical condition treated. ARD, adjusted risk difference; CI, confidence interval.

CI, −1.53 to 12.28). A sensitivity analysis using a random-effects model was consistent with the primary analysis.

Figure 3 shows the ARDs per 1000 population and corresponding 95% CIs for the overall population and by the clinical conditions treated. The point estimates for mortality for the clinical conditions of febrile neutropenia, pneumonia, and skin and skin structure infections favored comparators. These were post hoc subgroup analyses, and the numbers of deaths and patients in some clinical conditions (eg, skin structure infections) were relatively small (6/335 for cefepime vs 0/165 for comparators). The point estimates for mortality for intra-abdominal infections and urinary tract infections favored cefepime.

For the subgroup analysis by comparator antibacterials, 5 groups were prespecified as follows: ceftazidime, piperacillin-tazobactam, imipenem-meropenem, ceftriaxone-cefotaxime, and "other" (eg, mezlocillin, mezlocillin-gentamicin, cefuroxime, sulbactam-cefoperazone, clindamycin-gentamicin, and amikacin). Results of this analysis are shown in Figure 4.

***Patient-level analysis.*** We were able to obtain patient-level data from 39 trials. Patient-level data from 4 of these trials were not used in the final patient-level meta-analysis per our statistical analysis plan because these trials included fewer than 10 patients in at least 1 of the treatment arms (Figure 2). Therefore, 35 randomized, comparative trials were available for the patient-level analysis, with a total of 5058 cefepime-treated patients and 3976 comparator patients.

Table 2 gives the number of trials and patients by treatment group and clinical condition treated. Patients with febrile neutropenia, intra-abdominal infection, and pneumonia were the largest groups, comprising 15.52%, 11.14%, and 10.13% of the study population, respectively. Cefepime- and comparator-treated patients were similar with respect to demographic characteristics (eg, age, sex, and race) and baseline study characteristics (eg, pathogen recovered at baseline, pathogen susceptibility, and malignant neoplasm type) (Tables 3 and 4).

Overall, 285 (5.63%) of 5058 cefepime-treated patients died within 30 days, compared with 226 (5.68%) of 3976 comparator patients. Meta-analysis of these 35 trials did not show a statistically significant increase in mortality in cefepime-treated patients (ARD per 1000 population, 4.83; 95% CI, −4.72 to 14.38). Subgroup analyses by demographic characteristics did not demonstrate significant mortality differences between cefepime- and comparator-treated patients.

Additional post hoc subgroup analyses were performed. Thirty-day, all-cause mortality in US trials with patient-level data was 4.36% (144/3299) for cefepime-treated patients and 4.70% (121/2593) for comparator patients (ARD per 1000 population, 1.59; 95% CI, −9.21 to 12.38). Thirty-day, all-cause mortality in non-US trials with patient-level data was 8.01% (141/1759) for cefepime-treated patients and 7.59% (105/1383) for comparator patients (ARD per 1000 population, 11.49; 95% CI, −6.77 to 29.75). Figure 5 displays an additional subgroup analysis for US and non-US trials according to whether the clinical condition treated was FDA approved or not.

***Febrile neutropenia trials.*** The ARD per 1000 population in the subset of 24 febrile neutropenia trials included in our

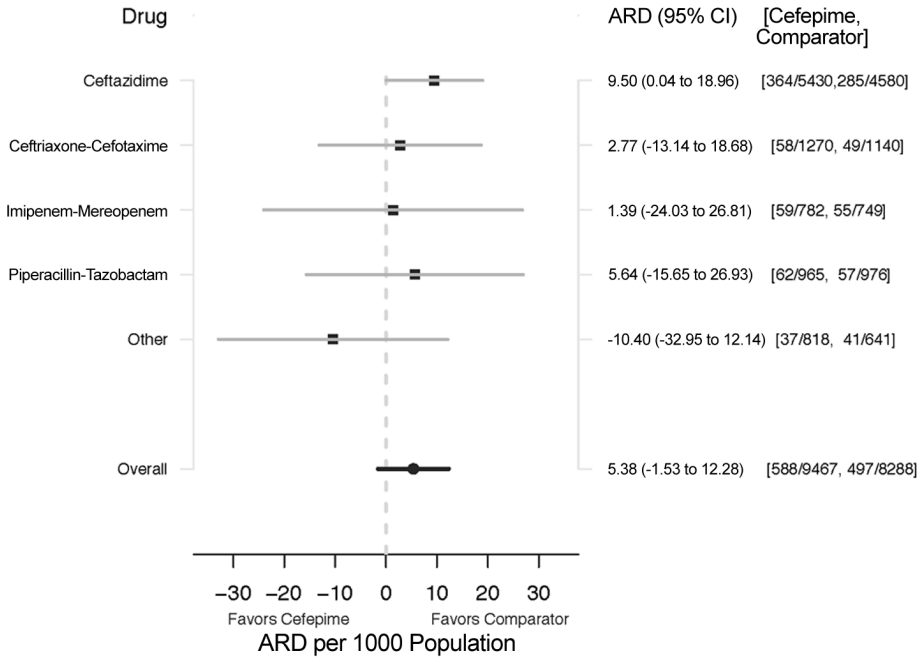


**Figure 4.** Trial-level meta-analysis (fixed-effects model) of randomized controlled trials of cefepime versus comparator, with mortality rate as a common endpoint. Figure shows the results by comparator drug. ARD, adjusted risk difference; CI, confidence interval.

trial-level meta-analysis was 9.67 (95% CI, −2.87 to 22.21). Because the Yahav et al [3] 2007 trial-level meta-analysis had reported relative risk rather than ARD per 1000 population, we estimated the ARD per 1000 population for the subset of febrile neutropenia trials (19 publications) in their meta-analysis to be 18.99 (95% CI, 4.96–33.02). Thirty-day, all-cause mortality rates for the 7 febrile neutropenia trials with patient-level data were 7.86% (61/776) for cefepime-treated patients and 6.55% (41/626) for comparator-treated patients (ARD per 1000 population, 18.10; 95% CI, −9.22 to 45.42). Exploratory subgroup analyses by baseline malignant neoplasm type showed that patients with solid tumors had greater mortality in the cefepime group, compared with comparators (ARD per 1000 population, 69.74; 95% CI, 8.13–131.35); however, the 95% CI is wide because of the low event rate and small number of patients (mortality rate, 10.45% [14/134] for cefepime and 3.70% [5/135] for comparators). No significant mortality differences were observed between cefepime and comparators for other malignant neoplasm types or baseline risk factors in the febrile neutropenia trials.

## DISCUSSION

Our analysis did not demonstrate statistically significantly higher 30-day, all-cause mortality rates in cefepime-treated patients, compared with those treated with other antibacterial drugs in randomized controlled trials. This finding was consistent in both trial-level and patient-level analyses. Although not statistically significant, the point estimates in the overall population and in several subgroups, notably the subset of febrile neutropenia trials, did not favor cefepime. The results of the subgroup analyses should be interpreted with caution given the caveats of post hoc subgroup analyses, the small numbers of patients, and the few deaths in these subgroups. On the basis of our analysis of patient-level data and CRFs, we did not identify a biologically plausible explanation for increased risk of mortality in cefepime-treated patients.

Our overall findings were not consistent with the trial-level meta-analyses published by Paul et al [2] in 2006 and Yahav et al [3] in 2007. The 41 publications in the Yahav et al [3] 2007 meta-analysis were based on 38 trials; our trial-level meta-analysis included these 38 trials plus 50 additional trials that

**Table 2. Trials by Clinical Condition Treated in the Patient-Level Data**

| Clinical condition | No. of trials | No. (%) of patients | |
|---|---|---|---|
| | | Cefepime | Comparator |
| Febrile neutropenia | 7 | 776 (15.34) | 626 (15.74) |
| Intra-abdominal infection | 5 | 585 (11.57) | 421 (10.59) |
| Pneumonia | 4 | 609 (12.04) | 306 (7.70) |
| Urinary tract infection | 4 | 426 (8.42) | 242 (6.09) |
| Skin structure infection[a] | 2 | 335 (6.62) | 165 (4.15) |
| Other | 13 | 2327 (46.01) | 2216 (55.73) |
| Total | 35 | 5058 (100) | 3976 (100) |

[a] Not differentiated by uncomplicated versus complicated skin and skin structure infections.

**Table 3. Baseline Demographic Characteristics in the Patient-Level Data**

| Characteristic | Cefepime ($n$ = 5058) | Comparator ($n$ = 3976) | Total ($n$ = 9034) |
|---|---|---|---|
| Age | | | |
| 0–17 years | 474 (9.37) | 448 (11.27) | 922 (10.21) |
| 18–54 years | 2114 (41.80) | 1547 (38.91) | 3661 (40.52) |
| 55–64 years | 820 (16.21) | 597 (15.02) | 1417 (15.69) |
| ⩾65 years | 1650 (32.62) | 1384 (34.81) | 3034 (33.58) |
| Missing data | 0 | 0 | 0 |
| Mean ± SD (range), years | 49.32 ± 23.64 (0.09–100) | 49.59 ± 24.46 (0.13–101) | 49.44 ± 24.00 |
| Sex | | | |
| Female | 2299 (45.45) | 1772 (44.57) | 4071 (45.06) |
| Male | 2759 (54.55) | 2204 (55.43) | 4963 (54.94) |
| Missing data | 0 (0) | 0 (0) | 0 (0) |
| Race | | | |
| Asian | 10 (0.20) | 13 (0.33) | 23 (0.25) |
| Black | 727 (14.37) | 563 (14.16) | 1290 (14.28) |
| Hispanic | 785 (15.52) | 595 (14.96) | 1380 (15.28) |
| White | 3212 (63.50) | 2637 (66.32) | 5849 (64.74) |
| Other | 45 (0.89) | 24 (0.60) | 69 (0.76) |
| Unknown | 279 (5.52) | 144 (3.62) | 423 (4.68) |
| Region | | | |
| United States | 3299 (65.22) | 2593 (65.22) | 5892 (65.22) |
| Outside the United States | 1759 (34.78) | 1383 (34.78) | 3142 (34.78) |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. SD, standard deviation.

were not included in their analysis. These 50 trials included 5517 cefepime-treated patients and 4484 comparator-treated patients. We successfully obtained additional mortality data for 11 of 16 publications for which mortality data were not available in the 2007 Yahav et al [3] meta-analysis. Subset analysis of 38 trials included in our meta-analysis and the 2007 Yahav et al [3] meta-analysis showed an increased risk of mortality between cefepime-treated and comparator patients (ARD per 1000 population, 17.02; 95% CI, 5.54–28.50), whereas the subset analysis of the 50 trials that were included in our meta-analysis but not the Yahav et al [3] 2007 analysis did not show a statistically significant difference in mortality (ARD per 1000 population, −2.8; 95% CI, −11.47 to 5.80).

We examined the distribution of patients by clinical conditions treated to further understand the differences between the subset of 38 trials included in the Yahav et al [3] 2007 meta-analysis and the subset of 50 additional trials included only in our analysis. In the 38-trial subset (included in both the 2007 Yahav et al [3] and our meta-analyses), there was a larger proportion of patients with febrile neutropenia (53.4%), compared with 14.5% in the 50-trial subset (included only in our meta-analysis). The subset with 50 additional trials included 7 trials (628 cefepime-treated patients and 470 comparator patients) in which cefepime was evaluated for the treatment of intra-abdominal infections. The Yahav et al [3] 2007 meta-analysis did not include any intra-abdominal infection trials, probably because these trials did not meet their predefined inclusion criteria of either a $\beta$-lactam comparator alone or combination therapy that included the addition of the same antibacterial to both treatment groups [3]. We included these trials in our analyses because we were evaluating the overall risk and benefit of cefepime use across all clinical conditions. The additional 50-trial subset included 15 trials in patients with "other" infections, such as bacterial meningitis, bacterial endocarditis, and bloodstream infections (2162 cefepime-treated patients and 2122 comparator patients), accounting for 40% of the population in this data set. In contrast, in the Yahav et al [3] 2007 meta-analysis, the "other" infections category accounted for 15% of the total population (7 trials, 560 cefepime-treated patients, and 562 comparators).

Regarding the analysis of febrile neutropenia trials, the statistically significant result noted by Yahav et al [3] in their analysis of 19 febrile neutropenia publications was not observed in our meta-analysis of 24 febrile neutropenia trials. Of note, only 2 of the 19 febrile neutropenia publications included in the Yahav et al [3] 2007 trial-level meta-analysis had statistically significantly increased mortality with cefepime use [22, 23].

Other authors have explored the risk of mortality in cefepime clinical trials [23–27]. In September 2009, Gomez et al [24] noted that interim mortality data from a febrile neutropenia

**Table 4. Baseline Study Characteristics in the Patient-Level Data**

| Characteristic | Cefepime ($n$ = 5058) | Comparator ($n$ = 3976) | Total ($n$ = 9034) |
|---|---|---|---|
| Any pathogen recovered at baseline | | | |
| No | 1864 (36.85) | 1470 (36.97) | 3334 (36.91) |
| Yes | 3194 (63.15) | 2506 (63.03) | 5700 (63.09) |
| Unknown | 0 (0) | 0 (0) | 0 (0) |
| Pathogens isolated at baseline treatment (susceptible) | | | |
| No | 246 (4.86) | 180 (4.53) | 426 (4.72) |
| Yes | 2216 (43.81) | 1587 (39.91) | 3803 (42.09) |
| Unknown | 2596 (51.32) | 2209 (55.56) | 4805 (53.19) |
| Fungal pathogen recovered at baseline | | | |
| No | 4303 (85.07) | 3313 (83.32) | 7616 (84.30) |
| Yes | 133 (2.63) | 127 (3.19) | 260 (2.88) |
| Unknown | 622 (12.30) | 536 (13.48) | 1158 (12.82) |
| Baseline infection monomicrobial or polymicrobial | | | |
| Monomicrobial | 2217 (43.83) | 1665 (41.88) | 3882 (42.97) |
| Polymicrobial | 591 (11.68) | 446 (11.22) | 1037 (11.48) |
| Unknown or missing | 2250 (44.48) | 1865 (46.91) | 4115 (45.55) |
| Patient had central catheter at baseline | | | |
| No | 4374 (86.48) | 3421 (86.04) | 7795 (86.29) |
| Yes | 432 (8.54) | 319 (8.02) | 751 (8.31) |
| Unknown or missing | 252 (4.98) | 236 (5.94) | 488 (5.40) |
| Renal insufficiency or failure | | | |
| No | 2889 (57.12) | 2173 (54.65) | 5062 (56.03) |
| Yes | 1317 (26.04) | 1134 (28.52) | 2451 (27.13) |
| Unknown | 852 (16.84) | 669 (16.83) | 1521 (16.84) |
| Hepatic insufficiency or failure | | | |
| No | 4311 (85.23) | 3380 (85.01) | 7691 (85.13) |
| Yes | 6 (0.12) | 7 (0.18) | 13 (0.14) |
| Unknown | 741 (14.65) | 589 (14.81) | 1330 (14.72) |
| History of diabetes mellitus | | | |
| No | 3537 (69.93) | 2696 (67.81) | 6233 (68.99) |
| Yes | 585 (11.57) | 482 (12.12) | 1067 (11.81) |
| Unknown | 936 (18.51) | 798 (20.07) | 1734 (19.19) |
| Active cancer or malignant neoplasm (febrile neutropenic patients only) | | | |
| Solid tumor | 134 (2.65) | 135 (3.40) | 269 (2.98) |
| Hematologic malignant neoplasm | 544 (10.76) | 391 (9.83) | 935 (10.35) |
| Unknown or NA | 4380 (86.60) | 3450 (86.77) | 7830 (86.67) |
| Bone marrow transplantation (febrile neutropenic patients only) | | | |
| No | 400 (7.91) | 311 (7.82) | 711 (7.87) |
| Yes | 179 (3.54) | 128 (3.22) | 307 (3.40) |
| Unknown or NA | 4479 (88.55) | 3537 (88.96) | 8016 (88.73) |
| History of COPD | | | |
| No | 4461 (88.20) | 3548 (89.24) | 8009 (88.65) |
| Yes | 192 (3.80) | 159 (4.00) | 351 (3.89) |
| Unknown | 405 (8.01) | 269 (6.77) | 674 (7.46) |

**NOTE.** Date are no. (%) of patients. COPD, chronic obstructive pulmonary disease; NA, not applicable.

trial that they presented at a conference in 2001 were included in the Yahav et al [3] 2007 meta-analysis. In this trial, patients were randomized to receive either 2 g of cefepime every 12 h or 4 g of piperacillin-tazobactam every 8 h (both arms also received amikacin) [23]. Although, in the interim analysis, a statistically significantly higher mortality rate was seen in cefepime-treated patients, in their final analysis, no difference in 28-day, all-cause mortality was noted (7.8% [15/190] in the

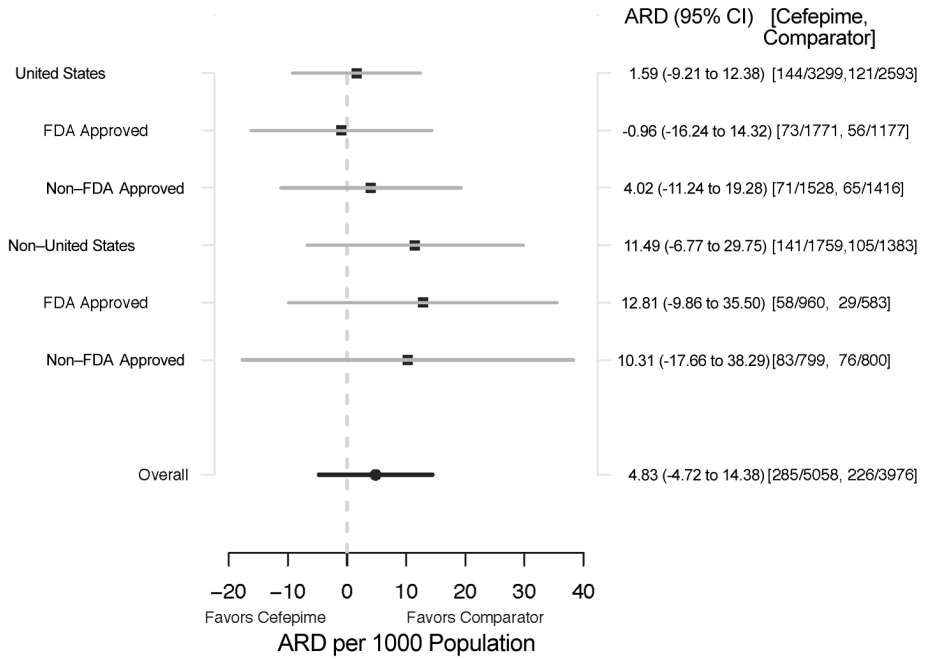


**Figure 5.** Subgroup analysis for US and non-US patients based on whether the clinical condition treated was approved by the Food and Drug Administration (FDA). ARD, adjusted risk difference; CI, confidence interval.

cefepime arm and 8.9% [17/190] in the piperacillin-tazobactam arm) [24]. Towne et al [25] reanalyzed mortality information from the 19 febrile neutropenia publications included in the 2007 Yahav et al [3] meta-analysis and were able to obtain information on the causes of death from 13 of these publications. They found no marked differences for infectious causes of death between cefepime-treated and comparator patients. They determined that none of the deaths were attributable to the antibacterial therapy administered and that more cefepime-treated patients died due to progression of underlying disease. In a retrospective cohort study of pediatric patients with acute myelogenous leukemia, Fisher et al [26] evaluated exposure to cefepime, ceftazidime, antipseudomonal penicillins, or carbapenems within the first year from acute myelogenous leukemia diagnosis. They found that cefepime exposure did not result in greater risk for in-hospital mortality when compared with other commonly used $\beta$-lactam antibacterials.

The strengths of our analysis included the following. First, because we were able to access data and results from unpublished trials submitted to the FDA for review and published studies, our meta-analysis included a larger number of clinical trials than did other published meta-analyses. Second, we obtained patient-level clinical trial data for a number of trials and were able to perform analyses based on these patient-level data in addition to those based on trial-level data. Third, the overall findings were consistent across both trial-level and patient-level analyses. For febrile neutropenia trials with patient-level data, we reviewed the CRFs of patients who died in an attempt to identify a biologically plausible explanation for the reported mortality difference. No biologically plausible explanation for a mortality imbalance was identified.

The limitations of our analysis included the following. First, most of the trials were open label. Second, the meta-analysis was not designed and did not have the power to assess mortality differences in several subgroups of interest, and as a result, the numbers of patients in subgroups with significant findings were small, making it difficult to interpret the results. Therefore, additional research will be necessary to explore potential differences in mortality for some of these subgroups. Third, because the "other" clinical conditions subset in the trial-level analysis included patients treated for a variety of infections, this population subgroup may have been more heterogeneous than others enrolled for treatment of specific conditions.

We did not find that the use of cefepime was significantly associated with increased mortality, compared with other antibacterial agents, for all trials included in our meta-analysis. Although the point estimate for the risk difference in the subset of trials including patients with febrile neutropenia did not favor cefepime, it was not statistically significant. Neither reviews of the CRFs nor analyses based on patient-level data identified a biologically plausible reason for an increased risk of mortality with cefepime use. Only adequately powered and well-controlled prospective trials may definitively answer the question of whether the use of cefepime, compared with other antibacterial agents, is associated with increased mortality.

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