Efficacy and safety of cefepime: a systematic review and meta-analysis

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Cefepime is a broad-spectrum cephalosporin with enhanced coverage against Gram-positive and Gram-negative bacteria. We did a systematic review of randomised trials that compared cefepime with another β-lactam antibiotic, alone or with the addition of a non-β-lactam antibiotic to both study groups. We searched Central, PubMed, Embase, Lilacs, new US Food and Drug Administration drug applications, conference proceedings, and references of the included studies. Two reviewers independently did the search and data extraction. 57 trials were included. All-cause mortality—the primary outcome—was higher with cefepime than other β-lactams (risk ratio [RR] 1·26 [95% CI 1·08–1·49]). Sensitivity analyses by the trials' methodological quality revealed higher RRs for trials reporting adequate allocation-sequence generation (1·52 [1·20–1·92]) and allocation concealment (1·36 [1·09–1·70]). Baseline risk factors for mortality were similar. No significant differences between groups in treatment failure, superinfection, or adverse events were found. This Review provides evidence and offers possible explanations for increased mortality among patients treated with cefepime in randomised trials.

Introduction

The cephalosporins are currently among the most widely prescribed class of antibiotics in hospitals.[1] Their broad spectrum of activity both against Gram-positive and Gram-negative bacteria and a low toxicity profile contribute to their widespread use.

Cefepime is a semi-synthetic, broad-spectrum cephalosporin classified within the fourth generation class.[2,3] Compared with ceftazidime, cefepime has enhanced activity in vitro against Gram-positive bacteria, including meticillin-sensitive *Staphylococcus aureus* and *Streptococcus pneumoniae*.[4] Cefepime has better activity against Gram-negative bacteria that produce extended-spectrum β-lactamase than other commercially available oxyimino-cephalosporins.[4–7] Cefepime's superior activity is attributed to more rapid penetration into bacteria, the targeting of multiple penicillin-binding proteins, or lower affinity for several β-lactamases.[3] This drug may have a lower propensity for selection of resistant (derepressed) mutants, which results in a lower rate of resistant phenotypes during or after treatment,[8,9] although failures have been reported.[10] Cefepime is currently widely used in hospitals for its approved indications, including empirical monotherapy for febrile neutropenia, pneumonia, bacteraemia, and urinary tract, abdominal, and skin or soft-tissue infections.[1,2,11]

In a previous systematic review that assessed empirical monotherapy for febrile neutropenia, we found an increased rate of mortality with cefepime compared with other β-lactam antibiotics.[12] The cause of the increased mortality was not clear. Superinfections were more frequent with cefepime compared with other β-lactams, but the difference was not statistically significant. No differences were observed within other secondary outcomes, including treatment failure. Subgroup analyses and meta-regression did not detect an association with specific bacteria.

We therefore did a systematic review of all randomised controlled trials that compared cefepime with other β-lactam antibiotics. The primary outcome was all-cause mortality. We aimed to expand our previous analysis to all cefepime trials, including patients without neutropenia, and to systematically extract patients' baseline characteristics, adverse events, and efficacy data in the search for an explanation for the increased all-cause mortality.

Methods

Inclusion criteria and outcomes

We included randomised controlled trials that compared cefepime with a different β-lactam antibiotic. The addition of a non-β-lactam drug (eg, aminoglycoside) was allowed as long as the same antibiotic and dose were used in both study groups.

The primary outcome assessed was 30-day all-cause mortality. If all-cause mortality was unavailable, mortality at end of study follow-up and up to 30 days was used. Secondary outcomes were as follows: clinical failure (defined as non-resolved infection, treatment modification, or death as a result of infection); microbiological failure (defined as failure to eradicate the causative pathogens); bacterial, fungal, and any superinfections (defined as new, persistent, or worsening symptoms with or without signs of infection associated with the isolation of a new pathogen or the development of a new site of infection); and adverse events.

Search strategy and selection criteria

We searched the Cochrane Central Register of Controlled Trials (Central), PubMed, Embase, and Lilacs databases. The search terms "cefepim*", "BMY-28142", "BMY-28142", "maxipime", "maxcef", "cepimax", "cepimex", or "axepim" were combined with the Cochrane filter for randomised controlled trials (except in Central).[13]

Unpublished trials were sought in references of all selected studies, relevant conference proceedings, trial registries and ongoing trial databases, new drug application documents of the US Food and Drug

Administration, and through personal contact with the investigators and sponsoring pharmaceutical companies of the included studies. No language or date restrictions were imposed. The last search was done in October, 2006.

Study selection and data extraction

Two reviewers (MP and DY, NS, or AF) independently did the search, applied inclusion criteria, and extracted the data. Outcomes were extracted preferentially by intention to treat, including all individuals randomised in the outcome assessment. If intention-to-treat data were not available, data per protocol were extracted and compared with intention-to-treat analysis through sensitivity analysis. For clinical failure, a modified intention-to-treat analysis was done by imputing failure for all dropouts. In all cases in which mortality data or randomisation methods were not reported in the primary reference, we requested the data from the investigators and the sponsor. Quality assessment was done using the individual component approach, which assessed allocation-sequence generation, allocation concealment, blinding, intention-to-treat analysis, and the number of patients excluded from the outcome assessment. Allocation concealment and generation were graded as adequate, unclear, or inadequate, by use of criteria suggested in the Cochrane handbook.[13] To assess the effect of study quality on outcomes, we did sensitivity analyses by individual components. Additionally, we compared patients' baseline characteristics that may have affected outcomes. For studies assessing patients with febrile neutropenia, we recorded age (in adults), neutrophil count, percentage of patients with acute leukaemia or bone-marrow transplantation, and percentage of patients with documented infections. For the other studies, we recorded age, temperature, percentage of patients with severe infection, and percentage with septic shock. We assigned 1 point for each risk factor to the group (cefepime *vs* comparator) in which it was more prevalent, and compiled the comparison between study groups for all trials.

Statistical analysis

Risk ratios (RRs) and 95% CIs were calculated for individual studies. Heterogeneity in the results of the trials was assessed using the chi-squared test for heterogeneity and the I^2 measure of inconsistency.[14] If no heterogeneity was found, meta-analysis was done using the Mantel-Haenszel fixed-effects model (Review Manager 4.2, Nordic Cochrane Centre). RRs of less than 1·0 favour cefepime for all comparisons. Comparisons were subcategorised by the comparator antibiotic and main diagnosis (eg, pneumonia, febrile neutropenia). Subgroup analyses for mortality and clinical failure were planned for Gram-negative, Gram-positive, and *Pseudomonas* spp infections, and pneumonia. Because outcome data for most of these subgroups were not available, meta-regression analysis was done to assess the association between the percentage of these infections and individual study effect estimates (STATA 8). A funnel plot was used to assess small study effects (eg, publication bias).

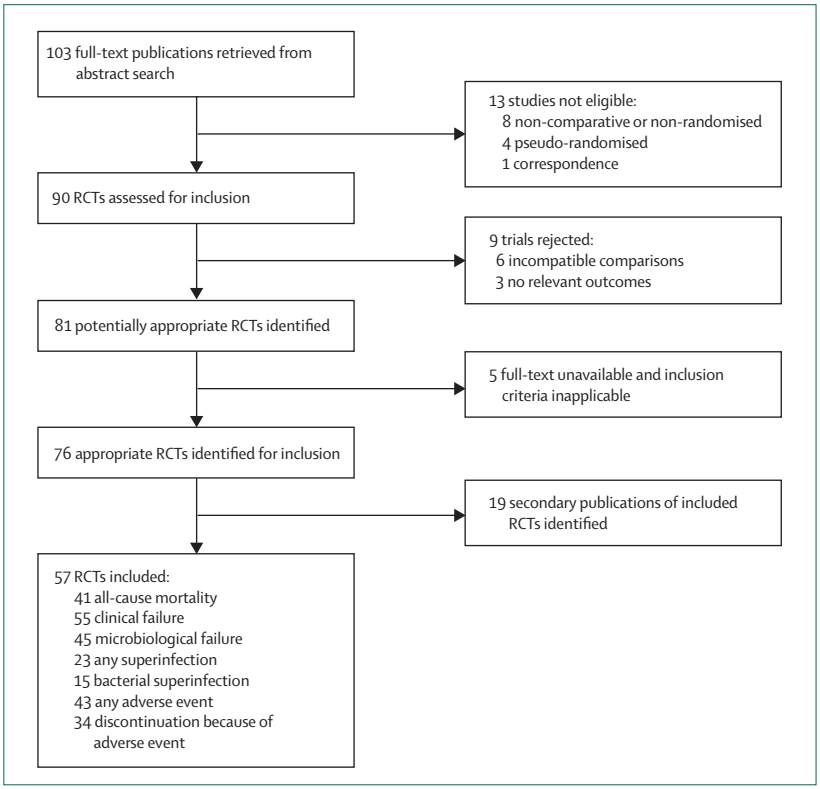

***Figure 1*: Trial profile**
Excluded studies and detailed reason for exclusion are shown in webtable 2. RCT=randomised controlled trial.

Results

The trial profile is shown in figure 1. 103 publications were retrieved for full-text inspection, of which 46 were excluded. 57 randomised controlled trials that compared cefepime with a different β-lactam antibiotic were included in the Review[15–70] (webtable 1). One publication described two trials.[50] The excluded trials and reasons for exclusion are shown in webtable 2.

See **Online** for webtable 1 and webtable 2

The trials assessed cefepime for many different indications (webtable 1). For febrile neutropenia, cefepime was compared with ceftazidime,[15,23,26,28,32,36,43,45,51,57,67] imipenem-cilastatin or meropenem,[19,25, 29, 56,66] piperacillin-tazobactam,[20,22,37,61] or ceftriaxone.[30] Aminoglycosides were added to both study groups in six trials[28,30,32,37,43,61] and vancomycin in one trial.[15] For pneumonia or lower respiratory tract infections, cefepime was compared with ceftazidime,[16,18,21,31,44,47,48,50,59,60] cefotaxime,[17,27,68] ceftriaxone,[38,70] cefoperazone-sulbactam,[42] or imipenem-cilastatin.[69] Other trials that compared cefepime with ceftazidime included patients with urinary tract infections, sepsis, bacteraemia,

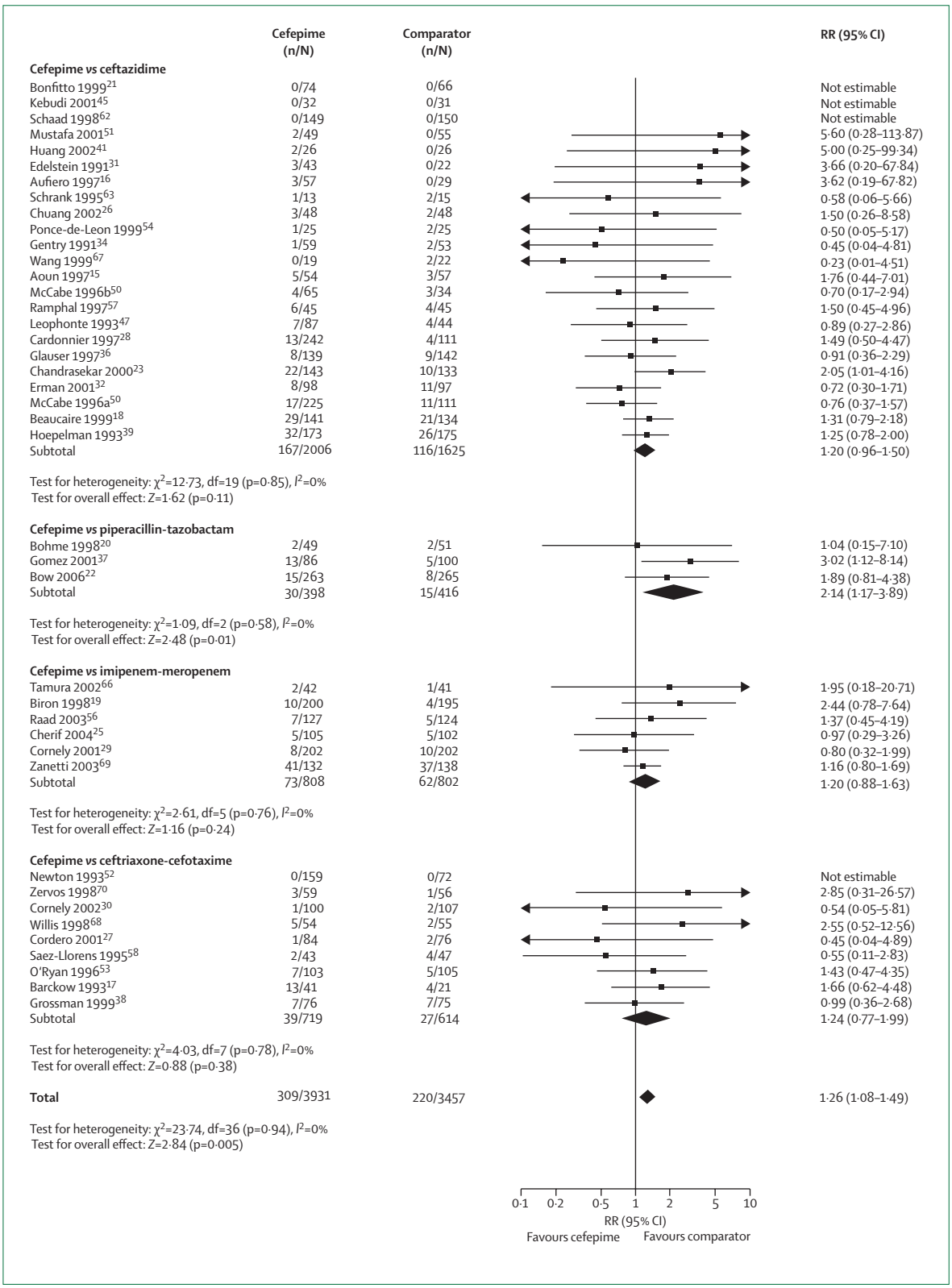

***Figure 2*: All-cause mortality by comparator drug**

Studies are identified by the name of the first author, year of publication, and reference. Fixed-effects meta-analysis used for estimation of combined risk ratio (RR; 95% CI). The comparison is subcategorised by the comparator antibiotic.

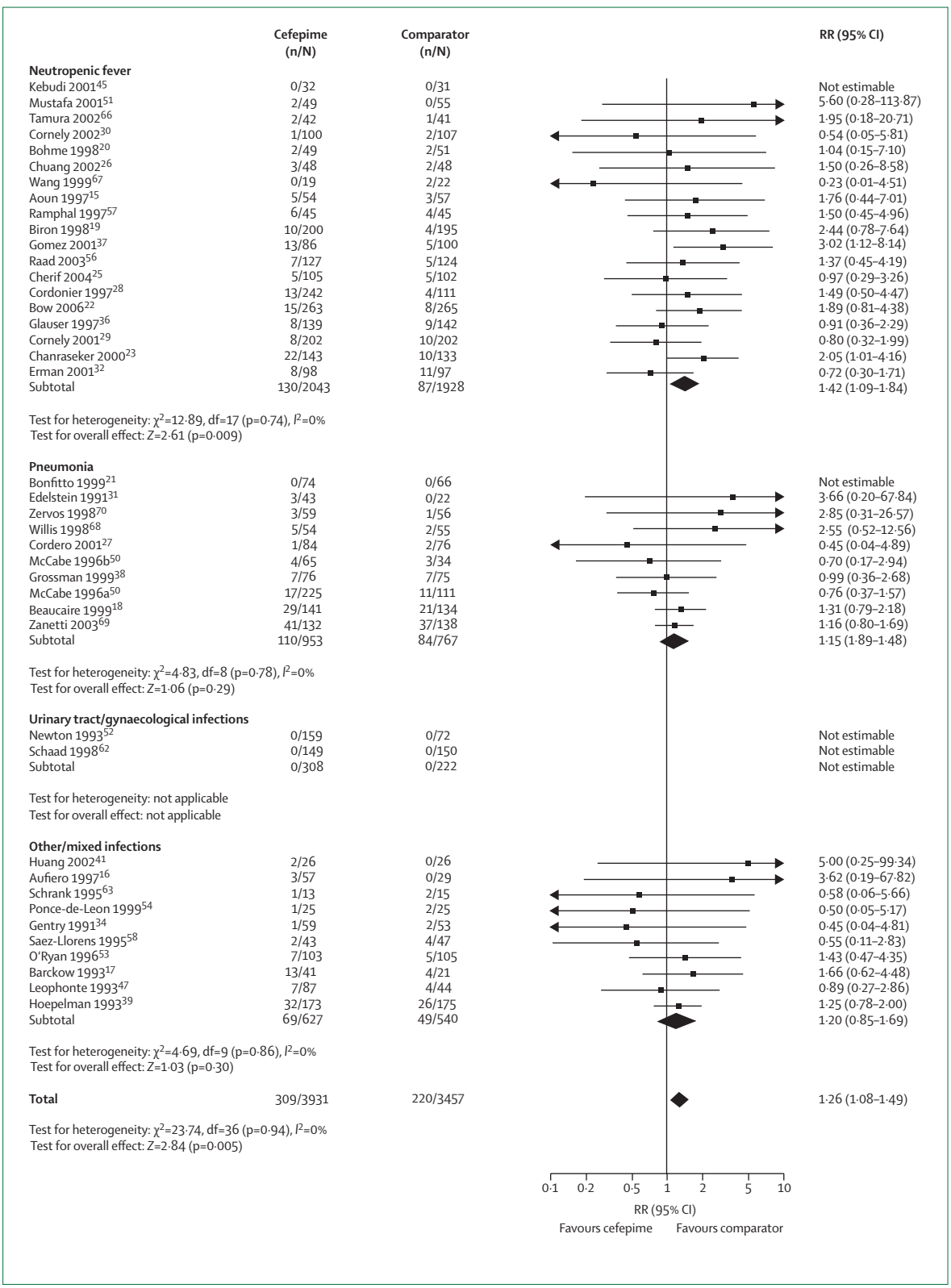

***Figure 3*: All-cause mortality by indication**

Studies are identified by the name of the first author, year of publication, and reference. Fixed-effects meta-analysis used for estimation of combined risk ratio (RR; 95% CI). The comparison is subcategorised by the main infectious diagnosis that defined patients for inclusion in the trial.

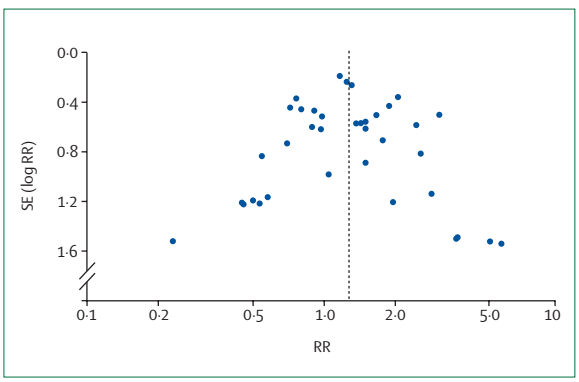

***Figure 4*: Funnel plot for all-cause mortality**
A plot of the trials' precision (SE of log [risk ratio (RR)]), as a measure of trial size, against RR on a logarithmic scale. The graph shows a symmetric, inverted funnel shape. Dotted line indicates combined effect estimate.

or skin or soft-tissue infections.[24,33,34,39,40,41,46,54,55,62,63,64,65] Three trials compared cefepime with ceftriaxone or cefotaxime for children with meningitis,[49,53,58] and one trial compared cefepime with cefotaxime for gynaecological infections.[52] The full daily dose most commonly used for febrile neutropenia was 6 g and for pneumonia was 4 g, although lower doses were assessed. Overall, 11723 patients were randomised in these trials.

Adequate allocation concealment and allocation-sequence generation were described in 30 trials (webtable 3). One trial was triple blind,[23] five were double blind,[38,50,55,59,60] outcome assessors were blinded in eight trials,[18,19,29,36,51,56,62,69] and the remaining were open-label trials. The score for baseline patient risk factors did not differ significantly in trials assessing febrile neutropenia (1·12 [0·70–1·79]; 18 trials) or among other trials (1·15 [0·71–1·85]; 26 trials).

See Online for webtable 3

All-cause mortality data were available from 41 trials (webtable 3; 7388 patients).[15–23,25–32,34,36–39,41,45,47,50–54,56–58,62,63,66–70] Mortality was significantly higher for cefepime than its comparators (1·26 [1·08–1·49]; p=0·005). No significant heterogeneity was detected for the overall comparison (p=0·94, I^2=0%). All antibiotic comparators were associated with lower all-cause mortality (figure 2), with significance shown for piperacillin-tazobactam (2·14 [1·17–3·89]; p=0·01). All-cause mortality was higher for cefepime in all types of infections, except for the subgroup with urinary tract infections in which no deaths occurred (figure 3). The difference in all-cause mortality was significant for febrile neutropenia (1·42 [1·09–1·84]; p=0·009).

Studies of higher methodological quality were associated with greater mortality for cefepime. Studies reporting adequate allocation concealment yielded a slightly higher RR (1·36 [1·09–1·70]) than studies in which concealment was unclear (1·16 [0·91–1·47]). Similarly, studies with adequate allocation-sequence generation had higher effect estimates than those with unclear generation (1·52 [1·20–1·92] *vs* 1·07 [0·86–1·34]). Blinding and type of analysis (intention-to-treat *vs* per-protocol analysis) did not affect the results.

The proportion of patients with microbiologically documented Gram-negative and *Pseudomonas* spp infections was 17–97% and 0–40%, respectively. All-cause mortality for these subgroups of patients was not available. The association between the percentage of these infections and the studies' RRs by meta-regression analysis was not significant. Post-hoc analyses showed no significant associations between trial results and the percentage of adverse events in the cefepime group or the cefepime dose used in the study. Exclusion of studies that compared cefepime with carbapenems (of broader coverage spectrum) did not eliminate the disadvantage observed for cefepime (1·29 [1·06–1·56]). Re-analysis of all studies by use of a random-effects model gave results that were similar to the fixed-effects model (1·24 [1·05–1·46]). The funnel plot for all-cause mortality showed studies to evenly distribute within an inverse funnel shape around the combined RR (figure 4), which indicated that publication bias was unlikely.

Clinical failure was assessed in all but two trials,[29,49] and these analyses included 8911 patients. Overall, clinical failure was similar for cefepime compared with the comparator drugs (0·98 [0·93–1·03]), and for the different indications (figure 5). No significant difference was found among the subgroup of patients with pneumonia or lower respiratory tract infections (0·92 [0·82–1·04]; 2427 patients). No significant differences between cefepime and ceftazidime (0·94 [0·88–1·01]), carbapenems (0·92 [0·79–1·07]), and ceftriaxone or cefotaxime (0·92 [0·76–1·11]) were detected. Risk of clinical failure was significantly higher for cefepime versus piperacillin-tazobactam (1·09 [1·01–1·18]; p=0·04).

Studies with adequate allocation concealment yielded an RR for clinical failure of 1·01 (0·95–1·07), whereas studies of unclear concealment methods showed a non-significant advantage for cefepime (0·93 [0·86–1·01]). Results were similar for adequate allocation generation (1·00 [0·95–1·05]) and double-blinded studies (1·01 [0·82–1·23]). A modified intention-to-treat analysis included 10786 patients and yielded an RR of 0·98 (0·95–1·02).

Microbiological failure was not significantly different for cefepime compared with the comparator drugs (0·92 [0·84–1·02]; 45 trials, 4574 patients). The RR for the comparison with ceftriaxone or cefotaxime was 0·87 (0·63–1·22; 11 trials, 1023 patients).

New infections after treatment with cefepime versus comparator drugs occurred with similar frequency in both study groups (0·96 [0·79–1·17]; 23 trials, 4032 patients). Similarly, there was no significant difference overall between cefepime and comparator drugs in the comparison of documented bacterial superinfections (1·01 [0·74–1·38]; 15 trials, 2502 patients).

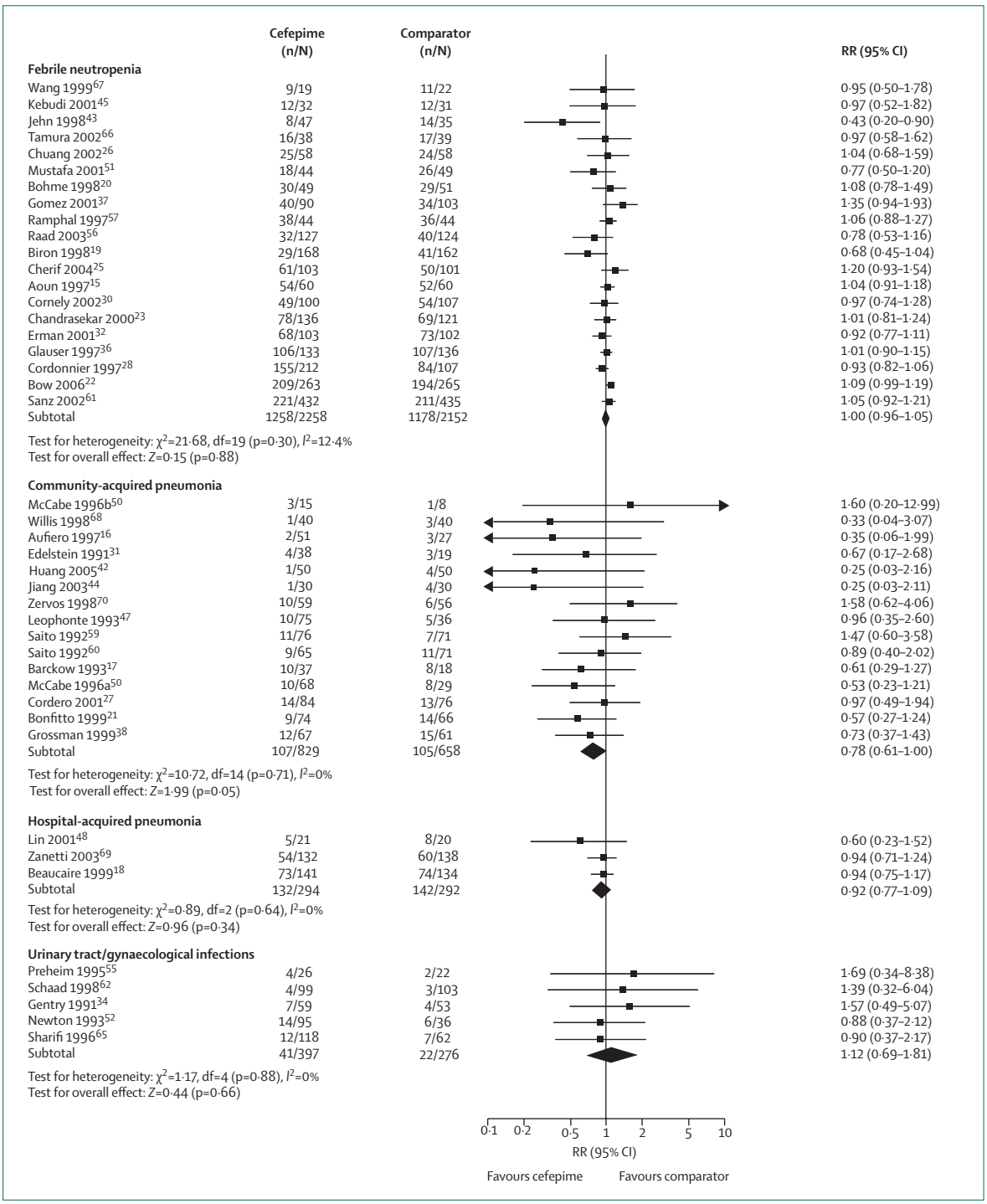

Figure 5 **(continued on next page)**

The frequencies of any adverse event (0·99 [0·94–1·04]; 43 trials, 8806 patients) and adverse events requiring discontinuation (1·20 [0·94–1·52]; 34 trials, 7305 patients) were similar for cefepime versus comparator drugs. Neurological complications (other than headache) were reported in 19 trials[18,22,25,27,28,38–41,47,52,55,56,59–62,65,68] (1·16 [0·78–1·13]). Seizures were reported in one trial and occurred in the imipenem group.[56]

Discussion

The objective of our systematic review was to assess the efficacy and safety of cefepime, nearly a decade after its

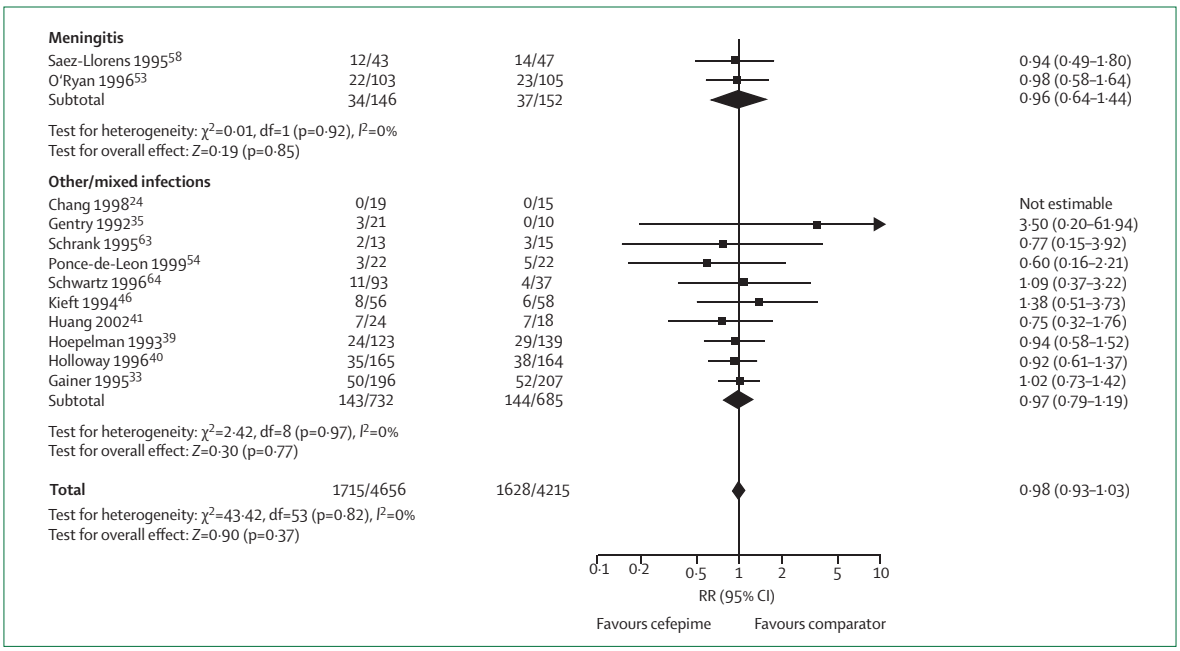

***Figure 5* (continued from previous page): Clinical failure by indication**
Studies are identified by the name of the first author, year of publication, and reference. Fixed-effects meta-analysis used for estimation of combined risk ratio (RR; 95% CI). Clinical failure is subcategorised by the main infectious diagnosis that defined patients for inclusion in the trial.

approval for clinical use.[2] We therefore compiled all randomised controlled trials that compared cefepime with a different β-lactam antibiotic. We allowed only the addition of a non-β-lactam antibiotic to both study groups, thus limiting the difference between study arms to the β-lactams compared.

We found all-cause mortality to be significantly higher with cefepime than with other β-lactams. The RR of 1·26 denotes an increase in all-cause mortality of 26%, with 95% CIs ranging from an increase of 8% to an increase of 49%. The corresponding number of patients needed to treat with comparator drugs in order to prevent one death with cefepime is 50 (33–100) patients, given a weight adjusted mortality rate in the comparator group of 5·8%. Further analyses of the mortality outcome and assessment of secondary outcomes did not reveal a specific cause for the increased mortality, nor a specific patient population at risk. Among subcategories of patients, significantly increased mortality with cefepime was seen only among neutropenic patients, but the RRs were similar for other types of patients and infections.

We selected all-cause mortality as the primary outcome because it is ultimately the most objective outcome and the main purpose of treating patients with infections. Other outcomes, such as clinical failure, are influenced by providers and outcome assessors, and may be prone to bias, especially in open trials that are assessing a novel broad-spectrum antibiotic. Even if assessed without bias, treatment failure is not a correlate of antimicrobial efficacy. Clinical failure is most often because of treatment discontinuation or modifications for various reasons by the treating physician. Microbiological eradication may represent antimicrobial efficacy more closely, but can be assessed only in the subgroup of patients with microbiologically documented infections, and does not always correlate with clinical improvement. Thus, the lack of a sensitive measure of efficacy in such trials requires all-cause mortality to be monitored and assessed.

In view of in-vitro and microbiological data from previous studies on cefepime, our results are somewhat surprising. Cefepime provides a broader spectrum of coverage in vitro than most comparator drugs assessed in these trials.[4] An advantage has also been claimed with regards to resistance induction, which should result in fewer secondary infections and better outcomes overall.[71] Therefore, how can our results be explained? A spurious finding is unlikely given the significance and homogeneity of our results. Moreover, several points support our findings on mortality. Studies of lower methodological quality tend to exaggerate spurious treatment effects.[72,73] In the case of our Review, studies of higher methodological quality were associated with the larger effect estimates. A 52% increase in mortality with cefepime was observed in studies reporting an adequate method for generation of the allocation sequence. To further assess the possibility that improper randomisation methods led to the assignment of sicker patients to the cefepime group (including studies in which randomisation methods were not reported) we compared patients' baseline characteristics. No significant differences were found. We combined studies comparing cefepime with different

antibiotics for different infectious diagnoses. However, examination of the forest plots and formal statistical methods indicate that no evidence of heterogeneity of effect estimates was present. Finally, the funnel plot was symmetric, pointing against the existence of small study effects, such as publication bias.

We offer two possible explanations for our results. The first is an unrecognised adverse event. Recent reports have described neurotoxic effects with cefepime, including encephalopathy and non-convulsive status epilepticus, which have resulted in the addition of this adverse event in the drug application and postmarketing experience of cefepime.[74–80] Most reports involve adults with acute or chronic renal failure, but cases of encephalopathy and status epilepticus have been reported in patients with normal renal function.[81,82] Non-convulsive status epilepticus can be difficult to recognise in elderly patients, particularly if there is no history of seizures.[83] Delay in diagnosis may result in increased morbidity or mortality.[84] Therefore, increased mortality in the cefepime group might be explained by undiagnosed cases of non-convulsive status epilepticus or encephalopathy. The second possible explanation is inadequate antimicrobial efficacy in vivo. Discrepancies between results in vitro and in vivo have been described with cefepime, explained by an inoculum effect, poor tissue concentrations, or pharmacodynamic considerations that favour continuous administration of cefepime.[85–89] Randomised controlled trials are limited in their ability to assess rare and previously unrecognised outcomes. Trials of antibiotic treatment are further limited by imprecise efficacy outcome measures. Either of the possibilities may exist and should be pursued.

The main limitation of this Review is the lack of complete mortality data. All-cause mortality was not reported in all studies. We complemented published data through correspondence with the primary investigators, but did not achieve complete data for all trials. Nearly all trials that reported financial support were sponsored by Bristol-Myers Squibb, the producer of cefepime. Confronted with preliminary results from our Review, the company did not supply further data or results for unpublished trials.[90–93] We could also not determine the reasons for increased mortality in these trials. Data extraction was explicitly planned to search for its cause, given results of a previous meta-analysis.[12] We thus planned to extract data on mortality for patients with specific types of infections and pathogens, but these data were not reported.

Conclusions

In view of the wide choice of alternative antibiotic treatments, the increased mortality observed with cefepime, whatever its reasons, should lead us to call for reconsideration of its use. Cefepime is currently recommended in several guidelines worldwide for the empirical treatment of febrile neutropenia,[94–97] severe community-acquired pneumonia,[98,99] and late-onset hospital-acquired pneumonia.[100] Interventions aimed at optimising antibiotic use in hospitals encourage the use of cefepime for these and other indications.[101–104] The new data presented in this report may necessitate a change in recommendations and in practice. Full mortality data must be obtained from all trials done to date. If mortality is indeed higher with cefepime, analysis of individual patients might clarify its reasons. Pending that, no new trials with cefepime for moderate to severe infections should be done.

Search strategy and selection criteria

These are described in detail in the Methods section on page 338.

Conflict of interests

We declare we have no conflicts of interests.

Acknowledgments

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