First, there may have been a publication bias against cefepime therapy. Indeed, data on mortality were not available for 16 trials (ie, 2180 patients). However, for the pooled relative risk for mortality to reach 1, the mortality rates in the comparator arms in these studies should have been 5 times higher than the rates in the cefepime arms (an unlikely occurrence). Second, inadequate randomization concealment methods could have led to (biased) allocation of cefepime to sicker patients. Our assessment of baseline patient characteristics did not reveal such differences. Finally, the difference could have been due to a true biological effect, whether related to efficacy or adverse events. Recent studies have shown that, in critically ill patients, only continuous doses of cefepime 6 g/day achieved adequate concentrations that were greater than the minimum inhibitory concentration, especially for patients with *Pseudomonas aeruginosa* infection [11–13].

In 43 randomized controlled trials, patients who were given cefepime died more often than patients who were given another β-lactam antibiotic (number needed to harm, 50; 95% confidence interval, 33–100). Unless convincing data are produced showing that this excess mortality is not related to cefepime, we would advise clinicians to avoid using the drug. Such data can be compiled from all trials looking at baseline patient characteristics and all-cause mortality, preferably on an individual patient level. These data were not divulged, although our analysis was first presented in 2006 and published in full in 2007.

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**Reply to Paul et al**

To the editor—We appreciate the feedback from Paul et al [1]. However, we do not think our concerns were satisfactorily addressed. We were never concerned about the statistical methods of the meta-analysis, which we thought were done professionally. However, we do have serious concerns about their assumptive conclusions and about the use of all-cause mortality to evaluate the safety of a drug in patient populations that had imminently high death rates due to rapid progression of the disease states, for which therapeutic response had been highly unpredictable.

Although the method used by Yahav et al [2] to assess the baseline values in the studies analyzed was appropriate, their demographic criteria might not have been. Paul et al [1] used the fixed selection of age, neutrophil count, percentage of patients with acute leukemia or who received a bone marrow transplant, and percentage of patients with documented infections to assess baseline characteristics for all febrile neutropenia studies and found no baseline difference. Many of the studies analyzed [3–10] used various selections of baseline characteristics that were relevant to the patients studied, including types of cancer (leukemia, lymphomas, myeloma, and solid tumors), stages of cancer, predisposing risk factors (mucositis, use of hematopoietic growth factors, and use of central line catheter), severity of neutropenia, and types of treatment (chemotherapy vs. radiation).

The statement by Paul et al [1] that, “in 43 randomized controlled trials, patients who were given cefepime died more often than patients who were given an-
other β-lactam antibiotic” was not all correct. Of the 4 subgroup analyses (ie, cefepime vs. ceftazidime, cefepime vs. piperacillin-tazobactam, cefepime vs. imipenem-meropenem, and cefepime vs. ceftriaxone-cefoxatome), only the cefepime versus piperacillin-tazobactam subgroup, which included 3 studies [5–7], was statistically significant.

Cases of neurotoxicity, which included encephalopathy and nonconvulsive status epilepticus, were used to explain the increased mortality in the cefepime group [2]. We could not find any description of a suspected case of neurotoxicity in the studies analyzed that could have contributed to the death of a patient in the cefepime group. However, Biron et al [6] reported 6 patients from the cefepime group who died of extensive cancer. Chandrasekar and Arnow [9] reported that 24 (75%) of 32 patients who died did so 11 weeks after the completion of the study. Attributing the difference in the deaths of those patients with cancer to rare case reports of toxicity, which have been reported among patients receiving β-lactams and/or carbapenems [11–13], did not make much sense, especially when the reported rates of adverse effects were similar between the 2 treatment groups in many studies analyzed [3–9].

Yahav et al [2] attributed inadequate antimicrobial efficacy in vivo to the increase in mortality. Their meta-analysis [2] found no difference in clinical failure between treatment with cefepime and treatment with the comparator drugs. Although their analyses “did not reveal a specific cause for the increased mortality” [2, p. 344], they insisted on finding reasons to explain the statistically significant difference in the mortality rates without providing much clinical evidence. Therefore, we raise the same question that Machtay et al [14] did 10 years ago: is meta-analysis really meta-physics? Meta-analyses should not be considered a substitute for well-designed trials [14]. What Yahav et al [2] concluded should not be taken as the final word.

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Is the Minimum Inhibitory Concentration of Vancomycin an Infallible Predictor of the Clinical Outcome of Staphylococcus aureus Bacteremia Treated with Vancomycin?

To the Editor—We read with interest the study of Soriano and coworkers [1] that described the relationship between the clinical outcome of *Staphylococcus aureus* bacteremia and the minimum inhibitory concentration (MIC) of vancomycin. In this prospective clinical study undertaken in a Spanish university hospital, it was observed that among 168 patients treated with vancomycin for an *S. aureus* bacteremia, a higher MIC of vancomycin (>2.0 mg/L) was independently associated with a significantly greater risk of death at 30 days (odds ratio [OR], 6.39; 95% confidence interval [CI], 1.68–24.3; *P* < .001), compared with an MIC of 1.0 mg/L. Interestingly, these findings, which led the authors to suggest the need for the evaluation of the possible superiority of new antistaphylococcal agents versus vancomycin when a strain has a vancomycin MIC >1 mg/L, are in clear contrast with those of a recent English study that par-