validity of guidelines requires an analysis of their recommendations—including early removal—and a comprehensive assessment of the reportedly beneficial outcomes that form the basis of these guidelines (Table 1).

The authors also suggest that our multivariate analysis does not answer the question of whether early removal affects outcome. Because our question was “whether early CVC removal…was associated with the beneficial outcomes that form the basis for current recommendations for early CVC removal” [3, p 296], we performed logistic regression analysis, a robust method for examining outcome predictors. Our consistent findings that early removal did not predict poor outcome answer our question convincingly. Surprisingly, the authors of both letters support current guidelines [4, 5], notwithstanding the fact that the concerns they raise about our analysis apply to many of the studies from which these guidelines were derived and despite their serious limitations, including small sample size, retrospective data collection, inclusion of patients without candidemia and/or without CVC, and no time points for early removal [3]. In contrast, our report examined the largest series of candidemia cases, predefined time points for early removal, and assessed 12 end points using prospective protocol-based evaluation. Our consistent findings across outcomes are a testimony to the robustness of our analysis.

How should our findings be interpreted at the bedside? The compelling evidence that we present that patients with candidemia are unlikely to suffer adverse outcomes if their CVC is not promptly removed provides clinicians with the opportunity to individualize their decision when managing diverse populations, instead of blindly following guidelines. Indeed, one size does not fit all.

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References

possible way of searching for trials introduced bias into the FDA meta-analysis. In trials that were published, with use of the FDA data, the relative risk for mortality associated with cefepime was 1.23 (95% confidence interval, 1.07–1.42; with no heterogeneity, $I^2 = 0$; ie, cefepime was significantly worse than other drugs). In the unpublished studies provided by the sponsor to the FDA, the relative risk was 0.80 (95% confidence interval, 0.66–0.97; with no heterogeneity, $I^2 = 0$; ie, cefepime was significantly better than other drugs), with a $P$ value <.05 for the comparison between published studies and data newly supplied by the sponsor in response to this investigation [1].

In simple words, cefepime, a lucrative drug, shows an excess mortality compared with other $\beta$-lactams in trials that were published. The sponsor writes to the authors of a systematic review that all data were published. The FDA asks the sponsor for additional data, and the sponsor produces data on 27 unpublished trials in which the mortality for patients treated with cefepime is significantly lower than for patients treated with other $\beta$-lactams, low enough to balance the published studies and reduce the relative risk to 1. The FDA officers (in response to e-mails and a phone call) are not interested in obtaining additional data on the said trials to make sure that they were performed, to ensure that they fit the question, and to determine their methodology.

The authors of the FDA analysis also conducted a patient-level meta-analysis on a subset of 35 studies selected by the sponsor, studies with no excess mortality among patients treated with cefepime. Twenty (57%) of the 35 studies were not published, compared with the 7 unpublished studies (30%; $P = .046$) of the 23 studies not included in the patient-level meta-analysis. What did the FDA expect to find in this subset of trials? It should be pointed out that possible explanations for bad outcomes associated with cefepime are accumulating [6–10]. In conclusion, we believe that a proper, critical, systematic review (and not only a meta-analysis of 4 columns of numbers) should be performed on the material presented by the sponsor. We also believe that a situation in which 27 trials on 1 drug were performed but not published or put in the public domain cannot be justified. The major investment in randomized controlled trials is not the funding money, but the goodwill and efforts of the participants and researchers. They participate because they are promised that the results will help people. This trust should not be betrayed.

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Reply to Leibovici et al

To the Editor—We thank Dr Leibovici and colleagues for their comments [1] regarding our evaluation of cefepime [2]. Although we agree that the challenges discussed highlight the importance of making all data pertaining to randomized controlled trials publicly available, their comments seem to reflect a misunderstanding regarding the methodology of our meta-analysis. The apparent assertion by Dr Leibovici and colleagues that our meta-analysis was simply based on data from a table of 88 trials provided by Bristol-Myers Squibb containing only a trial identifier, indication treated, number of participants, 30-day mortality, and comparator drug is incorrect.

The goal of our meta-analysis was to evaluate the overall risk versus benefit of cefepime with use of all available published and unpublished data. In our attempt to gather all available information on cefepime, we searched the literature and reviewed the publications that constituted the basis for the Yahav et al meta-analysis [3]. Second, we reviewed clinical trial data we had on file for cefepime. Third, we requested that Bristol-Myers Squibb provide detailed data on all cefepime trials to which they had access, including several datasets for our analysis. Last, we attempted to contact the authors