Cefepime and Death: Reality to the Rescue

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Cefepime is a broad-spectrum, fourth-generation cephalosporin originally approved by the US Food and Drug Administration (FDA) in 1996 for treatment of bacteremia, pneumonia, and other serious conditions and 1 year later as monotherapy in the empiric treatment of patients with fever and neutropenia. In the years after its approval, most physicians became confident of both the efficacy and safety of the drug.

However, in 2007 came a surprising turn of events. Yahav and colleagues published a meta-analysis of 38 randomized trials involving cefepime and found a statistically significant increase in the risk of death for cefepime-treated patients versus those treated with various comparator antibiotics [1]. The study was sufficiently persuasive to compel the FDA to issue an alert to clinicians to “be aware of the risks and benefits” of prescribing cefepime until a full review could be undertaken. The FDA then embarked on the arduous task of scrutinizing every available bit of clinical data to determine whether the drug indeed was unsafe.

In the 3 years that passed since the meta-analysis, however, clinicians were left in the lurch, unsure whether to trust our sense that cefepime seemed safe and effective or defer to the mysterious power of the meta-analysis, an approach that so few of us can comfortably argue against.

With the publication of the FDA cefepime “mega”-meta-analysis in this issue of Clinical Infectious Diseases, Kim and colleagues have now brought clarity and calm to the contentious debate [2]. In contrast to the findings of Yahav et al [1], they find no significant increase in mortality associated with cefepime.

Understanding how the confusion began requires digging deep into the details of the 2 analyses. The Yahav et al meta-analysis was a trial-level analysis, not a patient-level analysis; it began with 57 clinical trial publications, of which only 41 publications (encompassing 38 trials) could be analyzed: mortality data were missing from the remaining 16 publications. Compilation of these reports revealed an increase in 30-day, all-cause mortality among those who had received cefepime, compared with other β-lactams (risk ratio, 1.26; 95% confidence interval, 1.08–1.49). This difference was driven primarily by the subgroup of 19 trials composed of patients treated empirically for fever and neutropenia for whom the mortality difference was greatest (risk ratio, 1.42; 95% confidence interval, 1.09–1.84).

To explain the mortality difference, the authors invoked either an “unrecognized adverse event” or “inadequate antimicrobial efficacy.” Yet, their own analysis showed no difference in clinical failure, microbiological failure, or serious adverse events between cefepime and its β-lactam peers. Another author hypothesis, that cefepime may have caused excessive, yet clinically unnoticed, episodes of fatal encephalopathy or status epilepticus, did not square with most clinicians’ experience with the drug. Finally, the possibility that the drug was simply microbiologically ineffective was unconvincing to those who had prescribed it for serious infections.

Thus, despite a statistically significant mortality increase with cefepime and plenty of trial results, the conclusions of Yahav et al [1] were plagued by a plausibility gap. It simply made no sense clinically or biologically that a drug so structurally and pharmacologically similar to other cephalosporins should be so singularly harmful.

The current FDA analysis has addressed and, we believe, dismissed these concerns. The merit of their study lies in 2 key features. First, the authors had access to a vast data set of both published and unpublished clinical trials, amounting to
>17,000 patients, obtained from the pharmaceutical sponsor and from investigators. Indeed, they included information from 88 clinical trials—50 more than were available to Yahav et al [1]. Second, the FDA was able to examine patient-level data from >9000 of these cases and extract underlying patient diseases, specific pathogens and their susceptibilities, and patient comorbidities.

Using the larger data set, the FDA found no difference in death at 30 days between the cefepime and comparator groups in trial-level analysis (6.21% of cefepime-treated patients vs 6.00% of comparators) or patient-level data analysis, comprising 35 trials (5.63% of cefepime-treated patients vs 5.68% of comparators). It bears emphasizing that, although the point estimates given in Table 3 of Kim et al [2] did not favor cefepime in the overall analysis, there was no statistical significance associated with that value. In a study encompassing such a large patient cohort, this is extremely reassuring.

The most compelling information presented by Kim et al [2], however, was that obtained for trials comparing cefepime with other agents for empiric antibiotic therapy in neutropenic patients with fever. For more than a decade, cefepime has been extensively used and widely recommended, even FDA approved, for this indication. Kim et al [2] reviewed 24 fever and neutropenia trials, including updated information from the 19 originally examined by Yahav et al [1] and unpublished data. In this set of trials, no mortality difference was discerned. Among 7 fever and neutropenia trials with available patient-level information, the FDA group found that most fatalities in both the cefepime-treated and comparator patients appeared because of an underlying malignant neoplasm and/or comorbid conditions and not because of a drug-related adverse event or lack of antibacterial efficacy.

In the end, what have we gained from this 3-year-long adventure? First, we are indebted to Yahav and colleagues for demonstrating the scientific courage to present unpopular but statistically supported conclusions from their review. Second, as clinicians, we are reminded that we have the right to question results that do not necessarily match our clinical experience and to carefully consider all of the data before eliminating valuable therapies. Finally, we must thank Kim and colleagues at the FDA for diligently seeking the truth in the data and for fulfilling their mission to protect the public health by ensuring the safety and efficacy of human drugs licensed in the United States. It is nice when a government agency works so crisply.

**Acknowledgments**


**References**