Cefepime Therapy and All-Cause Mortality

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The findings of increased all-cause mortality associated with cefepime therapy reported in a 2007 meta-analysis by Yahav and colleagues in The Lancet Infectious Disease prompted an early communication by the Food Drug Administration (FDA). The FDA stated that it would review more safety data to further evaluate the risk of death to patients treated with cefepime.

The meta-analysis’ conclusion and the FDA early communication have stirred up debates in many institutions about how to properly adjust their antibiotic practice. Our review of the method of the meta-analysis (e.g., the method of data collection) raises questions about its conclusion; we call for additional review of the clinical data before any effort is made to limit or eliminate cefepime from the current practice guidelines. We make a number of recommendations on the appropriate use of cefepime therapy while awaiting further FDA advice.

Cefepime is included as one of the anti-pseudomonal agents in several Infectious Disease Society of America (IDSA) guidelines [1–3]. At our institute, cefepime has been utilized with good result in an effort to reduce the overuse of fluoroquinolones, broad-spectrum carabapenems, and piperacillin-tazobactam, in line with studies reported elsewhere [4, 5]. Compared with ceftazidime and cefotaxime, cefepime is suggested to have less β-lactamase induction property and, consequently, to promote less selective resistance [6]. It can therefore be used as a potential option in the treatment of susceptible extended-spectrum β-lactamase–producing bacteria, such as Klebsiella pneumoniae and Escherichia coli [7]. Premature elimination of cefepime from antibiotic selection would shift the overall utilization of antibiotics, with subsequent changes in the pattern of antibiotic resistance [8]. Our following discussion supports the effort of the US Food and Drug Administration (FDA) to further evaluate the risk and causes of death in patients treated with cefepime [9]. Our discussion also raises questions about the conclusion of the meta-analysis performed by Yahav et al. [10].

Yahav et al. [10] analyzed a total of 57 randomized, controlled trials that compared the use of cefepime with that of comparator drugs. The primary outcome that they assessed was 30-day all-cause mortality. Data on mortality at end of study follow-up and up to 30 days after treatment were used if the data on all-cause mortality were unavailable. Secondary outcomes included clinical failure, microbiological failure, superinfection, and adverse effects. All-cause mortality was significantly higher with the use of cefepime than with the use of other β-lactams (risk ratio, 1.26; 95% CI, 1.08–1.49). For the outcomes of treatment failure, superinfection, or adverse events, there were no significant differences among groups.

In the meta-analysis performed by Yahav et al. [10], the statistical significance of the all-cause mortality rate was noted in the subcategories “cefepime vs. piperacillin–tazobactam” and “neutropenic fever,” which were listed in figures 2 and 3 of Yahav et al. [10], respectively. The studies that demonstrated a notable difference in the mortality rates for these 2 subgroups were Gomez et al. [11], Bow et al. [12], Biron et al. [13], Chandrasekar and Arnow [14], and Sanz et al. [15]. We selectively discuss these 5 studies as possible confounding variables of the meta-analysis performed by Yahav et al. [10].

Including or excluding the above-mentioned studies should affect the results of the meta-analysis performed by Yahav et al. [10]. The overall mortality rates given in these studies varied significantly as a result of the reporting methods used and noninfectious causes of mortality determined. Analysis of a drug’s effect by use of all-cause mortality in combined patient populations with varying risk of death was potentially infeasible. Confounding factors that could affect the mortality rate include the types and stages of cancer, the responsiveness to chemotherapy, the adverse effects of intensive chemotherapy, and comorbid conditions.

The study by Gomez et al. [11] was reported in an abstract. They compared the efficacy of intravenous cefepime ther-
apy (2 g every 12 h) with that of intravenous piperillin-tazobactam therapy (4.5 mg every 8 h), both given concurrently with amikacin therapy, for 121 patients who had fever and granulocytopenia. They reported that 6 patients from the cefepime group died and that 2 patients from the piperillin-tazobactam group died. However, in their analysis, Yavah et al. [10] reported that there was a total of 186 patients in the study by Gomez et al. [11] and that 13 of the 86 patients from the cefepime group died and that 5 of the 100 patients from the piperillin-tazobactam group died. It is impossible to verify this discrepancy or to determine the causes of overall mortality from the abstract [11].

Bow et al. [12] compared the efficacy of empirical cefepime therapy (2 g intravenously every 8 h) with the efficacy of empirical piperillin-tazobactam therapy (4.5 g intravenously every 6 h) for 528 cancer patients with neutropenic fever. The primary outcomes of their study were the success rate at 72 h, the end of treatment, and the test-of-cure review among the modified intent-to-treat population. The number of deaths in the cefepime and piperillin-tazobactam groups were 15 (5.7%) and 8 (3%), respectively, including noninfectious causes. A limitation of the study by Bow et al. [12] was that the entry criteria permitted enrollment of a widely heterogeneous study population. Many of the variables analyzed in the logistic regression analysis were statistically significant. Those variables (which included the absolute neutrophil count at the end of treatment; the use of a central venous catheter; the use of hematopoietic growth factors concomitant with study entry; and the rates of hematological malignancy, acute leukemia, and lymphoma) could affect the overall mortality rate.

It should be noted that the large randomized trial by Sanz et al. [15] that compared the efficacy of empirical cefepime plus amikacin treatment with the efficacy of empirical piperillin-tazobactam plus amikacin treatment for 869 neutropenic febrile patients was included in the “therapeutic failure by indication” (illustrated in their Figure 5) but not in the “all-cause mortality” (illustrated in their Figures 2 and 3) analysis by Yavah et al. [10]. Success rates were similar between the group of patients who received cefepime plus amikacin (49%) and the group of patients who received piperillin-tazobactam plus amikacin (51%). However, there were 2 patients from the cefepime plus amikacin group who died and 8 patients from the piperillin-tazobactam plus amikacin group who died. Exclusion of those mortality rates from the “all-cause mortality” category should affect the results of the analysis.

Biron et al. [13] studied 400 febrile neutropenic cancer patients who were treated with either cefepime (2 g intravenously 2 times per day) or imipenem-cilastatin (1 g intravenously 3 times per day). The treatment response was assessed after 7 days, with a success rate of 79% for the cefepime group and 72% for the imipenem-cilastatin group; the difference was statistically significant (£0.001). Of the 14 patients who died, 10 were from the cefepime group, and 4 were from the imipenem-cilastatin group, as accounted in the meta-analysis by Yavah et al. [10]. Only 5 of these patients died of infection (3 from the cefepime group and 2 from the imipenem-cilastatin group); the other 9 patients died of other causes (6 patients from the cefepime group died of extensive cancer), which suggested a high level of heterogeneity in the patient population.

Chandrasekar and Arnow [14] compared the efficacy of empirical cefepime therapy with the efficacy of empirical ceftazidine therapy for 276 febrile neutropenic patients with cancer. Of note, 88 patients (42 in the cefepime group and 46 in the ceftazidine group) were not eligible for evaluation of therapy success. Of the remaining 101 patients in the cefepime group, 58 (57%) were successfully treated; of the remaining 87 patients in the ceftazidine group, 52 (60%) were successfully treated. This difference in successful treatment between the groups was not statistically significant (£0.77). The study reported an overall mortality rate of 15% (22 of the 143 patients died) for the cefepime group and 8% (10 of the 133 patients died) for the ceftazidine group (£0.06). Chandrasekar and Arnow [14] attributed none of the deaths to the administration of these agents, and they noted that 24 (75%) of the 32 patients who died did so >1 week after the completion of the study. The mortality rate within 2 weeks of the termination of the study was 8% for the cefepime group and 6% for the ceftazidine group. Only 3 patients from each treatment group died of the initially treated infection.

Because Yavah et al. [10] could not find a specific cause for the increased mortality or a specific patient population at risk, they offered 2 possible explanations. They suggested that unrecognized adverse events (such as encephalopathy and nonconvulsive status epilepticus) as well as inadequate antimicrobial efficacy in vivo might be the causes of the increased all-cause mortality rate. These explanations are not highly convincing.

First, as adverse events reportedly associated with cefepime therapy, encephalopathy and nonconvulsive status epilepticus were rare. Second, these conditions should not always result in death. Third, patients with severe renal failure—an important risk factor for the above-mentioned conditions [16–19]—were not included in the studies analyzed. In their meta-analysis, Yavah et al. [10] assumed that these conditions caused significant increased mortality, which is more a speculation than a plausible explanation.

The authors’ second explanation for the increased all-cause mortality was inadequate antimicrobial efficacy in vivo. The findings from the meta-analysis that showed no significant difference in therapeutic failures between cefepime and its comparators should already have been a strong argument against this suggestion.

The FDA suggests that healthcare providers who are considering the use of ce-
Cefepime should be aware of its risks and benefits [9]. For the time being, we recommend the following:

1. Clinicians should be cautious of using only the meta-analysis by Yahav et al. [10] to change current clinical practice or to call into question current IDSA guidelines. Cefepime usage should be consistent with current practice guidelines, institutional antibiograms, and indicated conditions.

2. Nursing, medical, and pharmacy staff should become more aware of the signs and symptoms of encephalopathy and nonconvulsive status epilepticus in patients who are being treated with cefepime. It should be noted that patients treated with cefepime did have higher rates of encephalopathy and nonconvulsive status epilepticus than did patients treated with other β-lactams [16–19]. The signs and symptoms of encephalopathy include delirium, acute confusion, impaired attention or memory, decreased alertness, and disorientation. The signs and symptoms of nonconvulsive status epilepticus include altered mental status with confusion, psychosis, lethargy, or coma.

3. The dosage of cefepime should be adjusted according to the patient’s renal function. One of the important risk factors for encephalopathy and nonconvulsive status epilepticus is a dosage of cefepime that is not adjusted for renal insufficiency [18, 19].

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References