The Role of Cefoperazone-Sulbactam for Treatment of Severe Melioidosis

SIR—We read with interest the recent article by Chetchotisakd et al. [1], which reported the results of a clinical trial comparing 2 regimens for treatment of severe melioidosis. The authors concluded that cefoperazone-sulbactam plus cotrimoxazole might be used as an alternative to treatment with cefazidime plus cotrimoxazole.

Since the late 1980s, several trials [2–5] have evaluated new medications for the treatment of severe melioidosis. However, with regard to reducing the mortality rate, none of these medications have been shown to be superior to cefazidime with or without cotrimoxazole. Chetchotisakd and colleagues found equivalent mortality rates among patients treated with the 2 studied regimens. However, they failed to point out that the mortality rates observed in their study (18% and 14%) were much lower than the rates of 30%–40% observed in previous studies of cefazidime (with or without cotrimoxazole) for treatment of patients with severe melioidosis [2–5].

The study by Chetchotisakd et al. [1] did not have sufficient power to detect significant differences in the efficacy of the 2 regimens. For example, the sample size for this trial would have had to have been 146 subjects per group to have 80% power to detect a 2-fold reduction in mortality rates between the 2 patient groups, as determined by use of Epi Info 2000 (Centers for Disease Control and Prevention). Similarly, the study is severely underpowered to provide statistical evidence of equivalent efficacy. Therefore, it is risky to recommend cefoperazone-sulbactam as an alternative to cefazidime on the basis of the results of this underpowered study.

Melioidosis affects mainly poor rural persons who live in tropical regions, and cost is a big issue when considering new treatments. We believe that Chetchotisakd and colleagues should have provided information regarding the cost of the 2 treatment regimens (including vitamin K injections) used in this study in order to give readers information on the financial implications of their recommendation.

Along with gram-negative enteric bacilli, oxacillin-susceptible Staphylococcus aureus and Burkholderia pseudomallei were regarded as the most common causes of community-acquired sepsis in northeastern Thailand [6]. If this is the case, a fourth-generation cephalosporin, such as cefepime, might be a useful alternative to cefazidime as empiric treatment for sepsis in that region. However, before recommending use of any fourth-generation cephalosporins, in vitro testing of their activity against B. pseudomallei and clinical trials involving patients with melioidosis would need to be performed. Therefore, we believe that cefazidime (with or without cotrimoxazole) should still be regarded as first-line therapy for patients with suspected or proven severe melioidosis.

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Reply

Str—We thank Apisarnthanarak and Little for their response to our article. We also appreciate the opportunity to respond to their comments.

There are 2 reasons why the mortality rates (18% and 14%) reported in our study [1] are lower than those in studies published elsewhere [2–4]. First, exclusion criterion number 2 [1] stated that patients who were likely to die within 24 h of admission to the hospital were excluded from our study; this was not a criterion in the other studies cited by Apisarnthanarak and Little [2–4]. Second, it is difficult to compare mortality rates associated a given disease at 2 hospitals. The study that compared ceftazidime plus cotrimoxazole with conventional drugs [5] was conducted in our hospital and found the same mortality rate (18.5%) as did our study; the other studies [2–4], however, were conducted in another hospital.

A larger sample size was planned, but the costs were prohibitive. Although it was not large, the 95% CI of the main finding was considerably precise. That is, it is meaningful to know that the possible mortality rate difference lies between −3.6% and 5.4%. Therefore, we provided a crude analysis to allow readers to follow the logic of the different mortality rates for the 2 drugs. We also showed the adjusted analysis, which took into account the baseline imbalance. Results of Kaplan-Meier survival analysis supplied additional insight, because this method uses the time to death. Our conclusion was based on the 95% CIs of the adjusted rate difference, not the P value, so it was unnecessary to demonstrate the difference of the 2-fold reduction in mortality rates between the 2 groups. The upper limit of the 95% CI is more important—that is, it was not clinically important that the alternative treatment could have yielded a mortality rate 5.4% higher than the rate for conventional treatment. We acknowledge that some persons may consider such a difference to be meaningful. Therefore, the issue of the study being underpowered is avoided, because we still recommend the standard treatment.

At the start of this study, the cost of ceftazidime (Fortum; GlaxoWellcome) was higher than the cost of cefoperazone-sulbactam (Sulperazon; Pfizer). Since then, local production has driven down the cost of ceftazidime. Now, the cost of ceftazidime at a dosage of 6 g per day (~$30 in US dollars) is lower than that of cefoperazone-sulbactam at a dosage of 3 g per day (~$40). The cost of 10 mg of vitamin K is $0.80—not a significant cost. We did not include the information in our original manuscript so that readers would compare the local costs of the 2 regimens.

We agree that ceftazidime (with or without cotrimoxazole) is still the first line of treatment for patients with suspected or proven melioidosis. However, our study suggests that cefoperazone-sulbactam plus cotrimoxazole should be considered as an alternative treatment, especially for use as empirical treatment when Staphylococcus aureus is also being considered as a pathogen. Ceftazidime has limited activity against S. aureus [6, 7], unlike cefoperazone-sulbactam [7] (MIC90 of cefoperazone-sulbactam, 4 μg/mL; MIC90 of ceftazidime, 24 μg/mL).

In our unpublished in vitro data, cepipime, a fourth-generation cephalospo-

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