Reply to Zhou and Wu, “Be Careful with Adverse Events Caused by Cefoperazone-Sulbactam”

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We thank Drs. Zhou and Wu for their interest in our recent publication entitled “Randomized noninferiority trial of cefoperazone-sulbactam versus cefepime in the treatment of hospital-acquired and health care-associated pneumonia” (1) and appreciate comments they made on it. The recruited patients in this trial were allocated to subpopulations for intent-to treat (ITT), per-protocol (PP), and safety analyses.

All patients ($n = 166$) who received at least one dose of either cefoperazone-sulbactam or cefepime were included for safety analysis. Of those, 12 patients were excluded before entering the ITT subpopulation ($n = 154$) because of either violation of the study protocol or withdrawal from the study under the patient’s or their family’s request, and therefore, no follow-up information was available for outcome evaluations. Given these missing outcome data, we admit that the ITT analysis in this article would be better defined as a modified ITT with an explicit statement about postrandomization exclusions (2, 3).

As antibiotic therapies for a minimum of 7 days for hospital-acquired pneumonia (HAP) and health care-associated pneumonia (HCAP) have been widely accepted and recommended (4, 5), only recruited patients who underwent antibiotic therapy for ≥ 7 days rather than all the patients in the ITT subpopulation were included for clinical success (cure or improvement) evaluation at the test-of-cure visit, as was shown in Table 2 (1). Table 1 summarized baseline characteristics of patients who were evaluable for clinical success in the ITT subpopulation.

Permutated block randomization with an allocation ratio of 1:1 generating the random assignment of subjects was performed before this study. An independent

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statistician was responsible for generating randomization codes, and each random assignment was put in a sealed, opaque, and numbered envelope. The recruited patients were randomly assigned by a sequentially numbered envelope to different treatment arms to receive either intravenous cefoperazone-sulbactam or cefepime therapy. The study design and experiment were definitively and completely randomized. With the exception of the body mass index (BMI [kg/m^2]) (cefoperazone-sulbactam arm, 20.1 ± 3.6 versus cefepime arm, 21.4 ± 4.6 ; $P = 0.048$), statistically nonsignificant differences in baseline characteristics were found between patients from the ITT subpopulation allocated to different treatment arms and subjected to clinical success evaluation. Of note, between patients from the PP subpopulation allocated to the cefoperazone-sulbactam arm and the cefepime arm and included for clinical success evaluation, all baseline demographic and clinical characteristics, including BMI (cefoperazone-sulbactam arm, 20.0 ± 3.4 versus cefepime arm, 21.5 ± 4.5 ; $P = 0.058$), were not statistically significantly different. Given this, it is plausible that there was a type I error for $\alpha = 0.05$ for comparison of the BMIs between different treatment arms in the ITT analysis (6).

Based on the difference in BMI between treatment arms for clinical success evaluation in the ITT analysis, Zhou and Wu raised the question of whether the difference in BMI might lead to meaningfully different antibiotic concentrations in these patients' blood streams, thereby affecting the mortality rate. Overweight and obese individuals were reported to be at significantly higher risk of acquisition of pneumonia but were at lower risk of pneumonia mortality, which was referred to as "obesity survival paradox" (7); the paradoxical phenomenon has not been fully understood, and proposed explanations included that the metabolic reserves in overweight and obese individuals suffering pneumonia better counteract the increased catabolic stresses (7). Of note, in previously published studies, BMIs were categorized (e.g., underweight, normal BMI, obesity, and morbid obesity) for assessment of the clinical outcomes of the pneumonia patients (7). One meta-analysis revealed that an increase in $5 \text{ kg}/\text{m}^2$ of BMI reduced pneumonia mortality by 5% (relative risk of 0.95, with 95% confidence level of 0.93 to 0.98; $P < 0.01$) (7). It is not evident that the difference in clinical outcome between the cefepime and the cefoperazone-sulbactam arms in the ITT analysis in our series was confounded by the difference in BMI of $1.3 \text{ kg}/\text{m}^2$ (1); the BMIs of both arms belonged to the same categorized one. Results of clinical success rates in both the ITT and PP analyses in this study evaluating therapeutic effects against HAP/HCAP supported the conclusion that cefoperazone-sulbactam was noninferior to cefepime. Among the overall adverse events, serious adverse events (15.2% versus 5.7%; $P = 0.224$) and mortality rate (37.8% versus 18.2%; $P = 0.281$) were found to be higher in the cefoperazone-sulbactam arm than in the cefepime arm, and yet, they were statistically nonsignificantly different.

In summary, our data suggested that cefoperazone-sulbactam is noninferior to cefepime in treating HAP/HCAP; we concur with Zhou and Wu that the safety profile of cefoperazone-sulbactam needs to be consolidated by further study with a larger sample size.

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