Reply to Huang et al

To the Editor—We thank Drs Huang, Pastagia, and Chiang for their interest in our work and for the observations raised.

Concerning possible patient heterogeneity, we recall that most patients (70%) had ventilator-associated pneumonia. Whether an improved outcome may occur with colistin-rifampin combination in specific settings such as intra-abdominal infections, meningitis or bloodstream infections remains to be addressed. In planning the study, we valued the severity of patient clinical conditions rather than the actual primary site of infection. Indeed, in real life, Acinetobacter baumannii is often isolated in a specific individual from multiple sites (eg, lung, urine, blood, and feces), either simultaneously or during the hospital course. Furthermore, patients were rather homogeneous in terms of the severity of their illness. Their mean Simplified Acute Physiology Score (SAPS) II score was 40.2, with a standard deviation of 11.2, and only 4 patients had a SAPS II score <20. Thus, we believe our cohort was sufficiently homogeneous for a pragmatic clinical study.

The second point raised was the use of concomitant antibiotics that may have influenced the primary outcome. It should be noted that the administration of concomitant antibiotics was highly variable in terms of timing (ie, temporal relation to or overlap with the course of study drugs) and duration for individual patients. Therefore, it is very hard to analyze the effect and draw meaningful conclusions from the evaluation of concomitant antimicrobial therapies. In our view, the pragmatic nature of the trial, as well as the high clinical complexity of the study setting, leave narrow space for post hoc analyses. Moreover, all extensively drug-resistant A. baumannii strains isolated in this study—and endemic in our country—showed high-level resistance to meropenem (minimum inhibitory concentration, ≥16 mg/L) [1]. Therefore, meropenem could not be considered as potentially effective in vivo. Finally, the actual proportion of patients who received tigecycline was very low (n = 16; 7.9% of the overall cohort). Nonetheless, we agree that the issue of concomitant use of other antimicrobial agents that could have had an effect on extensively drug-resistant A. baumannii—including, for instance, glycopeptides—remains interesting. However, we would like to stress that concomitant use of additional antimicrobial agents is usually driven by concomitant infections with additional microorganisms and,
possibly, additional morbidity. In our study, some patients developed infection due to carbapenem-susceptible *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*. The incidence of these concomitant infection was similar in the 2 treatment arms.

We acknowledge that the absence of therapeutic drug monitoring is a shortcoming of our study. The fact that rifampicin may in theory modify the therapeutic effect of concomitant drugs, as our colleagues suggest, actually strengthens the idea that, in the absence of evidence for clinical superiority, rifampicin should not be added to colistin, at least routinely. Studies on the in vivo pharmacokinetics of colistin in the presence of rifampicin are lacking and would be useful.

As for the possible utility of rifampicin in a combination regimen with reduced colistin doses, we would like to underscore that most pharmacokinetic studies, published after our trial had begun, actually support the use of even higher doses of colistin than those we used [2, 3].

**Note**

*Potential conflicts of interest.* Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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