To the Editor—We thank Leung and Yew [1] for their insights into our study [2]. Although some benefit of micronutrient supplementation was observed among HIV-uninfected patients, it is noteworthy that a protective effect on a key primary end point of the trial—namely, short-term recurrences of tuberculosis (TB)—was stronger in the HIV-positive cohort.

We acknowledge that there could be some misclassification of early TB recurrences because of false-negative culture results at 1 month. This misclassification would be of potential concern if it were different by treatment arm. We would not expect differential misclassification given the randomized and blinded nature of our trial. Of note, among HIV-positive participants, the number with negative culture results at 1 month was somewhat larger in the micronutrients arm (n = 130) than in the placebo arm (n = 111). It could be argued that false recurrences after 1 month could have been more frequent in the micronutrients arm because of a larger number of false-negative culture results at 1 month; this could have spuriously inflated the treatment effect. To address this issue, we conducted supplemental analyses testing the effect of micronutrients on recurrences after 1 month after the initiation of treatment, regardless of the culture result at 1 month. Using this approach, the cumulative incidences of TB recurrence between 1 and 8 months were 23 of 193 and 12 of 201 in the placebo and micronutrients arms, respectively (relative risk, 0.50 [95% confidence interval, 0.26–0.98]). This indicates that culture misclassification at 1 month is unlikely to have affected the treatment effect we reported.

Our trial was not powered to specifically examine the effect of treating specific underlying nutritional deficiencies among patients with TB or to assess interactions between an overall indicator of nutritional status (such as body mass index) and treatment assignment on the outcomes studied. It would be informative to elucidate whether addressing specific nutritional deficiencies results in improved outcomes of infectious challenges. However, whether such an approach would yield benefits at the time of translating the findings of clinical trials into clinical practice is open to debate. In resource-limited settings, where TB and other infectious diseases are highly prevalent, multiple nutritional deficiencies usually coexist. In addition, the resources needed to assess specific nutritional deficiencies are seldom available at the patient level.

We agree that addressing the effect of nutritional interventions as adjunctive therapy to other antimicrobial treatments is an important future research endeavor.

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Potential conflicts of interest: none reported.

References

Ethical Consideration for Use of Carbapenems as Treatment for Sepsis Due to Carbapenem-Resistant Bacteria

To the Editor—A generally held medical principle is the avoidance of the use of an antibiotic for the treatment of an infection in which the pathogen has demonstrated in vitro resistance to the antibiotic, especially when alternative agents are available that could be expected to produce a better clinical outcome. Zhang et al. [1] recently published a study in which 2 experimental agents plus a carbapenem were compared with a carbapenem plus placebo for the treatment of sepsis due to organisms known to be resistant to carbapenem. Although the pub-
lished information from Zhang’s study is somewhat limited, it seems likely that effective antibiotic therapy (colistin, tigecycline, piperacillin/tazobactam, amikacin, etc.) could have been employed for at least some of the infections.

Treatment of significant systemic infections usually has a better outcome when appropriate antibiotics are administered as early as possible [2–5]. Continuing therapy with an agent known to have in vitro resistance to the pathogen while withholding treatment with an antibiotic known to have in vitro susceptibility appears to us to not be in the patients’ best interests. Both the Hippocratic maxim “do no harm” and the Declaration of Helsinki [6], in our opinion, seem to contradict the design and implementation of the study by Zhang et al., despite “ethical approval for the study” having been obtained from the local research ethics committee” [1].

Of concern also is the decision by the Journal to publish this work and thus co-author it to an aura of credibility. Peer-reviewed publications have a responsibility to uphold appropriate ethical standards.

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Reply to Cleveland and Gelfand

To the Editor—We agree with Cleveland and Gelfand [1] that ethical principles are paramount in the conduct of clinical research. In our study [2], we adhered to this practice. The carbapenem-resistant isolates in our study were also resistant to other available antibiotics in China, including piperacillin/tazobactam and amikacin. Tigecycline is not available in China, and colistin could not be used because of potential nephrotoxicity. Moreover, it was not known at the time when patients initiated the study that their organisms were resistant to carbapenems, and, thus, it was reasonable and ethical to randomize individuals to receive carbapenems plus either thymosin α₁ and ulinastatin or placebo. Once susceptibilities became known, if susceptible antibiotics had been available, they would have been used. As noted in our article, subjects received empirical antibiotic coverage for gram-positive bacteria, and antibiotics were adjusted when additional culture and sensitivity results became available. As also noted in the article, approval was obtained from the local research ethics committee before the study was initiated, and informed consent for participation was obtained from all patients or, if necessary, a relative. The trial was registered with the Chinese State Food and Drug Administration (Peking Science and Technology Development Plan 2002–641; registration number 2007Y0211).

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Editorial Comment

The ethical conduct of research is of the utmost concern to the Journal. In addition to the response shown above, the editors have requested and received from Zheng et al. a detailed document covering study design, informed consent, data analysis, quality control, and other issues, including the raw data for the article. An extensive list of the susceptibilities of individual organisms to the antibiotics available at the study sites can be found at the Journal’s Web site for this comment. On the basis of a detailed review of the authors’ responses and the additional data provided, the editors conclude that the clinical research reported in the published article was conducted ethically.

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