Nutrient Supplementation and Tuberculosis Treatment Outcome

To the Editor—We read with great interest the recent article by Villamor et al. [1] on the effect of micronutrient supplementation on tuberculosis (TB) treatment outcome as well as the accompanying editorial commentary by Benn et al. [2]. It is well known that TB is associated with being underweight [3]. Nutritional deficiency has also been found to be a negative prognostic factor in patients with miliary TB [4]. Being underweight at baseline [5] and the absence of early gain weight [6] have been associated with an increased risk of relapse in a large-scale TB treatment trial. However, relatively few studies have specifically examined the effect of nutrient supplementation.

The randomized controlled trial design, as rightly adopted by Villamor et al., is indispensable for obtaining a definitive answer regarding the role played by nutritional supplementation. However, as was pointed out in the accompanying editorial, micronutrients benefited HIV-uninfected subjects the most in Villamor et al.’s trial, whereas the opposite was the case in a previous trial in Tanzania [7]. Differences in case mix and study design could be contributing factors.

In anti-TB chemotherapy, bacteriological cure with the absence of relapse is probably the most clinically relevant end point. Although it is generally acceptable to use validated surrogate end points, such as 2-month culture conversion [8] or time to culture conversion [9], to decrease the sample size requirement and to shorten the duration of follow-up in explorative trials, caution has to be exercised in the employment of less-well-characterized end points, such as culture reversion after a single negative sputum culture result during the first month. Minor variation in sputum-collection technique and/or sputum processing could have produced a single negative culture result when the bacillary load was low after a month of treatment. When multiple end points and subgroups are evaluated in a single trial, results should also be interpreted with care.

Given that TB is generally more prevalent in developing areas and that nutritional supplementation is likely to show the greatest effect among those with malnourishment, an adequately powered trial will probably have to be implemented in a resources-limited area. Although specific nutrients might play a role, the overall nutritional status as reflected by body mass index also appears to greatly influence the risk of TB [3]. It is, therefore, necessary to study the effects of—or at least control for—the effect of overall nutritional status in nutrient-supplementation trials. Careful documentation of the overall nutritional status, in addition to specific nutrient deficiencies, is desirable, so that a maximum amount of information can be extracted from these often-costly trials.

The interaction between nutritional status and TB is complex. TB is also well known for its wasting effects. Dietary supplementation may fail either because of poor adherence or overwhelming disease effect. It may, therefore, be useful to monitor the relevant nutritional parameters during the intervention. Because sustained inflammatory disease activity may negate the effect of simple nutrient supplementation, at least in some patients, the role played by adjunctive corticoste-roids might also merit reappraisal. Indeed, such treatment has been found to afford earlier and more significant body weight gain, albeit with no differences in sputum bacteriological conversion and disease relapse rate [10].

Anti-TB drug resistance is an increasing concern globally. With our currently limited armament, it might be difficult to work out an effective regimen for those patients who have extensively drug-resistant TB. Because only 1 in 10 infected persons, on average, will ever develop disease in his or her lifetime, host factors appear to be critical in the defense against the tubercle bacillus. In situations where we are almost back to the prechemotherapy era, it might also be worthwhile to reexamine the role played by nutritional supplementation, either alone or as an adjunct to chemotherapy and/or surgery, in the humanitarian and active management of TB disease in these unfortunate patients.

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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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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-