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Prognostic Significance of Early Weight Gain in Underweight Patients with Tuberculosis

The most certain, albeit labor-intensive, way to delineate relapse of tuberculosis (TB) after apparently successful treatment is by regular culturing of sputum for mycobacteria up to at least 18 mo after cessation of chemotherapy. Surrogate markers employed in clinical trials of TB chemotherapy to assess the sterilizing capacity of the drug regimens in reducing relapse (1) include: (1) the proportion of patients with positive sputum cultures after 2 mo of therapy; (2) the speed of sputum culture conversion to negativity as measured by a survival analysis using Kaplan-Meier plot and the log-rank test; (3) the speed with which the viable mycobacterial count is reduced during the bi-exponential phase of bacillary killing, as measured by serial sputum colony-forming units during the first 1 to 2 mo.

In resource-limited program settings with a high burden of TB, these assessment tools can be a “white elephant.” Thus, a readily identified marker or predictor of TB relapse risk becomes a genuine necessity. An underweight condition at baseline was shown to be independently associated with relapse risk among HIV-negative patients with TB in a randomized chemotherapy trial, in addition to sputum culture positivity after 2 mo and cavitation on chest radiograph (2). In this issue of the *Journal* (pp. 344–348), Khan and coworkers (3) further demonstrate the prognostic significance of early weight gain among underweight patients with TB in the same trial. In their stratified analysis, the 2-yr relapse rates were 4.2%, 11.9, and 20.3% among those not underweight, those underweight but gaining > 5% weight at 2 mo, and those underweight and not gaining weight, respectively. In a multivariate analysis, lack of early weight gain was found to be an independent predictor of relapse in underweight patients with TB (odds ratio, 2.4; $p = 0.03$), after controlling for other risk factors including, among others, cavitation and sputum culture positivity at 2 mo. A relapse rate as high as 61% occurred among those $\geq 10\%$ underweight at diagnosis, and 62% of the relapses in this group in turn occurred among those patients failing to gain > 5% weight in the induction phase of treatment.

A previous study in Tanzania (4) concluded that weight gain during TB therapy was an unreliable indicator of overall treatment response. However, that study, besides including HIV-infected subjects, only analyzed weight change with bacteriologic status. It did not specifically look during the induction phase at the effect of early weight change on subsequent relapse rate among patients who were underweight at diagnosis. Indeed, in the study by Khan and coworkers (3), only the early weight change, and not the later or total weight change, was found to have an effect among underweight patients, which was independent of cavity or culture status. Such a specific association also suggests something more than purely the effect of nutrition status on the development of disease (5, 6). Among patients who might have lost substantial weight because of the illness, effective control of the pathogen in the induction phase is pivotal to the success of the currently employed short-course regimen, and

weight gain is likely an independent indicator of clinical response, in addition to culture conversion.

Despite the sizeable number of subjects in that trial (3), the sample size was barely sufficient using relapse as endpoint, especially after stratification. Because of resource constraints, the sputum smear alone is the main monitoring tool for treatment progress for the TB control programs in developing countries. As body weight has been well reported to be associated with risk of disease (5, 6), severity of disease (7, 8) and the response to treatment (7, 9), it is surprising that little attention has been paid to such a readily measured and inexpensive marker. As the World Health Organization is currently reviewing the TB program forms, it might also be worthwhile to consider this area in light of the recent data (3). If such a relationship between body weight and outcome can be reproduced in large TB programs under diversified service settings, this relatively simple finding could be translated into very significant clinical benefits, especially in the resource-limited settings.

With the prognostic significance of weight gain (3), it might also be relevant to explore other means to decrease the risk of relapse in underweight patients, aside from the prolongation of TB chemotherapy. Early increase in nutritional intake has been shown to increase body weight, total lean mass, and physical function (10). Nutritional supplementation might be relatively easy through introduction of financial aid and incentives as part of the holistic care for patients during TB chemotherapy (11). Furthermore, in many developing countries, the often inculcated perception of nutritional importance in TB would facilitate acceptance of implementation of enhanced nutrition (12). The role of corticosteroids, perhaps among selected patient populations, might also merit reappraisal, since such treatment has been found to afford earlier and more significant body weight gain, albeit no differences in sputum bacteriological conversion and disease relapse rate (13, 14). It would be interesting to assess whether weight gain achieved through nutritional or pharmacologic intervention could lead to similar reduction of relapse risk as weight gain observed naturally.

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