Does My Patient Have Multidrug-Resistant Tuberculosis?

Kwonjune J. Seung
Division of Global Health Equity, Brigham and Women’s Hospital, Boston, Massachusetts, and Partners In Health, Maseru, Lesotho

(See the editorial commentary by Fitzwater et al, on pages 371–378.)

After how long in tuberculosis (TB) treatment can I expected my patient to have negative smear or culture results? This is a common concern of clinicians throughout the world. One worry is about the infectiousness of the patient with TB. A patient who is smear negative can be expected to be less infectious than one who is smear positive, and this may indicate that he or she is safe to reenter the home and society. However, an even greater worry is about drug resistance, especially in an era when multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains are increasingly common. In developing countries, most TB is still treated empirically, without the benefit of drug susceptibility tests (DSTs). In these settings, failure to respond to first-line TB drugs is the only way to identify patients at risk for MDR TB. The question posed is a crucial one when evaluating a patient who is still smear positive after completing 2 months of treatment. Is the patient just a slow converter or does the patient have MDR TB?

A study by Fitzwater et al [1] published in this issue of Clinical Infectious Diseases sheds some light on this issue. It was conducted under program conditions in Peru, whose well-functioning national TB program has attained extremely high rates of patient adherence throughout TB therapy. Peruvian national TB control policies generally follow World Health Organization (WHO) guidelines, as do most middle- and low-income countries, and use a standardized regimen of first-line drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) for treatment of all patients with new TB. In addition to smear microscopy, which is commonly used for treatment monitoring in such settings, the study also included culture in liquid media, which is the most sensitive way to culture mycobacteria from sputum. The monitoring schedule was weekly for the first month, then every 2 weeks thereafter, which is frequent considering the study was conducted in an outpatient clinical setting. Finally, the study included a significant proportion of patients with drug-resistant TB, enough to analyze as a separate subgroup.

Overall, 90% of the patients were smear negative after 47.5 days of treatment. This finding was largely consistent with previous studies conducted in a variety of inpatient and outpatient settings showing that approximately 85%–90% of patients with TB can be expected to be smear negative after 2 months of treatment. However, in the subgroup analysis, drug resistance was strongly associated with delayed culture conversion. By 2 months, 90% of the patients with fully drug-susceptible TB had become culture negative. However, for patients with MDR TB, even by the end of the study, only approximately one-third of the patients had become culture negative. This proportion is particularly low considering that the group of patients with MDR TB who showed culture conversion likely included at least some who received appropriate therapy with second-line TB drugs based on their DST results.

Despite the strong association with drug resistance, however, smear conversion was not helpful for deciding which patients were likely to have MDR TB. According to WHO recommendations, national TB programs generally define treatment failure as positive sputum smears after the fifth month. According to this study, such patients are almost certain to have MDR TB, but waiting for so many months is beneficial neither for the patient nor for the public health. Shortening the cutoff to 2 months lowers the positive predictive value; in this study, two-thirds of patients who were smear positive at 2 months had MDR TB. Although this proportion is high, most clinicians would be reluctant to start second-line TB drugs empirically at 2 months without additional clinical evidence of treatment failure, such as continued cough, fever, and weight loss.

Even worse, 75% of the patients with MDR TB in this study were smear negative at 2 months and would therefore be missed completely by a screening protocol.
based on smear microscopy. The predominance of smear-negative, culture-positive MDR TB is likely due to the “fall and rise” phenomenon that occurs during inadequate TB treatment [2]. These patients were still infectious and unlikely to be cured because they were excreting viable drug-resistant mycobacteria in their sputum. At the end of the fourth month, the proportion of patients with smear-negative MDR TB actually increased. Under typical program conditions, where only smear microscopy is available for monitoring, most patients with MDR TB would be expected to be discharged as programmatic cures, quickly relapsing with smear-positive sputum within several months [3, 4].

Much of the current TB control strategy is still based on the old paradigm that all new cases are pan-susceptible and that drug resistance is “acquired” through non-adherence. The most recent WHO global survey on MDR and XDR TB clearly shows the limitations of this old paradigm. Rates of MDR TB have reached heights that were unimaginable 10 years ago, in both new patients and previously treated patients. In 12 countries, MDR TB rates have increased above 6% in new cases, meaning that MDR strains have become so widespread that large numbers of healthy people are becoming exposed and infected [5]. Meanwhile, TB control policies have continued largely unchanged, still recommending empirical first-line TB treatment without DSTs for all new TB cases.

Universal DSTs for all new patients with TB are often dismissed as impractical and cost-ineffective, but as MDR TB and XDR TB become more widespread, this is rapidly becoming the only logical public health strategy. For drug-resistant TB, just as for drug-susceptible TB, the best type of infection control is early diagnosis and treatment. Restricting DSTs to those who continue to be smear positive after a trial of first-line TB treatment is unlikely to decrease the transmission of MDR TB in the community. Many patients with MDR TB will die before their conditions are diagnosed, and others will have extensive disease that is less likely to respond to treatment. Furthermore, drug-resistant strains are likely to acquire additional resistance mutations the longer they are treated with inadequate regimens—a phenomenon called the “amplifier effect of short-course chemotherapy” [6].

This study should not be considered definitive; it should be repeated in other countries and other patient populations, especially human immunodeficiency virus–positive patients, who may have a different bacteriologic response to TB therapy. Nevertheless, studies such as this one illustrate the need for new research efforts to evaluate and challenge our old TB control paradigms. During the past 10 years, TB has changed the rules of the game, whereas our policies have stayed the course of wishful thinking. New public health policies based on scientific evidence are urgently needed to combat the growing scourge of drug-resistant TB.

Acknowledgments

Potential conflicts of interest. K.J.S.: no conflicts.

References