EDITORIAL

Challenges related to TB testing and diagnosis

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Juzar Ali, MD, FRCP(C), FCCP

Historically, a multifaceted approach to control tuberculosis across the globe has placed emphasis on increased implementation of the Directly Observed Treatment Short-course, or DOTS, designed to cure TB in communities with high incidence. According to WHO, more than 2 billion people (about one-third of the world's population) are estimated to be infected with *Mycobacterium tuberculosis*. In 2014, 9.6 million individuals became ill with TB, and 1.5 million died. In 2013, 9 million people worldwide became sick with TB disease, most of whom (80%) live in one of 22 high-burden countries.

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With an 86% cure rate of active TB cases worldwide, the commitment of national TB control programs must focus on identification of infected individuals in low-burden countries. To address this, newer, more rapid diagnostic tools and broader therapeutic options (especially for difficult-to-treat and multidrug-resistant cases) have been adopted, where available. However, these successes notwithstanding, there is still a long way to go.

 Juzar Ali

Despite our progress, the delivery of comprehensive patient-centered health care delivery remains challenging both in the resource-rich, low-TB incidence countries and in resource-limited, high-incidence countries. The disconnect between public TB control programs and private health care, the isolation of primary care from public health in health care delivery, the generally inadequate access to health care, and the discordance between individual patient care and programmatic disease management can best be depicted in the comorbidities associated with TB. In this context, TB and HIV, and TB and diabetes, stand out as glaring examples where targeted screening for TB should be considered a priority at all points of care and contact with patients.

There is now an increased awareness that the landscape of TB epidemiology is changing and a newer paradigm is emerging that requires a broader outlook.

Identification of TB comorbidity cases in high-risk populations, in persons with compromised immune status, in migrant populations, and in contacts of active cases across the globe poses challenges and requires a very focused approach.

Testing for TB infection is warranted to identify individuals who are at risk for new infection as well as individuals at increased risk for reactivation due to associated high-risk conditions. With these considerations in mind, the importance and priority of identifying and promptly treating cases of active pulmonary and extrapulmonary diseases is incontrovertible. It is also imperative to focus on screening patients with a higher risk for reactivation, such as patients associated with cancer, solid-organ transplant, HIV infection, diabetes, patients on cancer chemotherapy or on immune-modulating drugs, tumor necrosis factor-alpha inhibitors for immunological conditions, and those with a chest radiograph demonstrating evidence of old fibrotic diseases.

TB testing options

Testing options for TB include the tuberculin skin test (TST) and interferon (IFN)-gamma release assays (IGRAs). In recent years, results from these testing modalities have shown that there are differences in their use in terms of accuracy and cost, and that these differences should be important considerations when designing screening programs in various clinical, institutional and public health settings. Both testing modalities evaluate cell-mediated immunity and do not distinguish TB infection from TB disease.

Tuberculin skin test — The TST uses purified protein derivate (PPD) administered by an intradermal injection to identify individuals with previous sensitization to mycobacterial antigens. This method stimulates a delayed-type hypersensitivity response mediated by T lymphocytes, which causes induration within 48 to 72 hours, at which time the test is read and responses evaluated by induration measurement.

Utility of the TST is limited by factors related to a high risk for false-positive and false-negative results, which are mainly due to variability in operator technique, poor follow-up of persons not returning for the reading of the test after 48 to 72 hours, inter-observer variation in reading the results, the impact of the history of bacille Calmette-Guérin (BCG) vaccination, endemicity of nontuberculous mycobacterial (NTM) infection in certain geographic areas, and immune anergy to the PPD. Although the upfront cost of the TST is much lower compared with IGRAs, the downstream costs associated with the follow-up of these cases, both in terms of direct expenditures and time of personnel, further adds to the limitation of its use.

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Interferon-gamma release assays — IGRAs are next-generation diagnostic tools for assessment of TB infection. They assess surrogate markers of *M. tuberculosis* (MTB) infection as indicated by a cellular immune response to purified membrane antigens of MTB. IGRA results can be available in 24 to 48 hours and do not require a follow-up visit for reading of results. MTB-specific antigens include early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10), which are encoded by genes located within the region of difference 1 segment of the MTB genome. The antigens are more specific for MTB than PPD as they are not expressed by any BCG vaccine strains or most species of NTM, other than *M. marinum*, *M. kansasii* and *M. szulgai*. More importantly, *M. avium* complex (MAC), the most common nontuberculous mycobacteria worldwide, does not express either ESAT-6 or CFP-10, and thus patients with MAC infection are IGRA test-negative.

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Two IGRAs are available in many countries — the QuantiFERON-TB Gold (QFT) test (Qiagen Group) and the T-SPOT.*TB* test (Oxford Immunotec). The QFT test is an enzyme-linked immunosorbent assay that uses peptides from three *TB* antigens (ESAT-6, CFP-10 and TB7.7) in an in-tube format to measure IFN-gamma production from cells contained in whole blood. The T-SPOT.*TB* test is an enzyme-linked immunospot assay performed on isolated and normalized peripheral blood mononuclear cells. The testing procedure requires that a standardized number of peripheral blood mononuclear cells are placed in each test well, even if the overall peripheral blood lymphocyte count is low. The standardized cell suspension is stimulated with ESAT-6 and CFP10 peptides. Results are reported as positive, borderline or negative based on the number of spots in the wells, which are a footprint of cellular IFN-gamma release. Both tests were approved by the FDA.

Advantages of IGRAs

IGRAs have specificity greater than 95% for diagnosis of TB infection. The sensitivity for T-SPOT.*TB* appears to be higher than for QFT or TST and may offer advantages in evaluating individuals with HIV and immunosuppressive conditions.

The 2010 CDC guidelines indicate that IGRAs are preferred for patients with history of BCG vaccination and for individuals from groups that historically have poor rates of return for TST reading, such as those in transient homes and homeless shelters.

Limitations regarding the use of IGRAs as a screening method have been reported in some studies where serial testing is required or has been done. There are many logistical, operational and patient-related immunological factors that may explain resultant high rates of reversions and conversions, and this issue remains a matter of continued review and study. However, the interpretation of IGRAs in the broader clinical context, the assessment of the clinical utility of the borderline category-quantified numerical results, and the incorporation of this in the T-SPOT.*TB* test may help in understanding the clinical significance of these conversions and reversions.

The significant advantages of using IGRAs for TB infection have been acknowledged and recommended in various national and international guidelines and protocols either independently or in a two-step process. TB screening and testing programs at the public health, institutional and patient level should incorporate this testing tool where applicable, and where the cost-effective considerations of different at-risk populations have to be kept in mind, especially in terms of convenience and ease of use. This approach may in turn benefit TB control programs as a whole.

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- **For more information:**

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- 1
- 2