

Case Presentation

The Use of Interferon-Gamma Release Assays in a Contact Investigation

Case History:

A 23 year old university student from Africa was diagnosed with active TB disease in April 2008. The patient presented with an infrequent productive cough and no other symptoms. His tuberculin skin test (TST) was 15mm and chest radiographs were abnormal. His sputum was acid-fast bacillus (AFB) smear negative but culture positive for *Mycobacterium tuberculosis*. His specimen was pansensitive and he was started on four drug therapy May 2, 2008. A contact investigation was started with his closest contact being a US-born roommate who was TST negative on initial testing. As a precaution, further close contacts were tested including 11 friends, 15 classmates and 5 professors. Initial and follow up testing found that 20/31 (64.5%) were TST positive. Although the patient was smear negative and coughed infrequently, the results suggested widespread classroom transmission, warranting expansion of the contact investigation to medium priority contacts and perhaps even the entire campus. The Heartland National TB Center (HNTC) was consulted for advice in expanding the investigation.

Upon further review, all of the TST-positive individuals were foreign born and all 6 US-born contacts (five professors and one roommate) were TST negative. Before the investigation was expanded, HNTC recommended that all foreign-born TST-positive contacts be tested with QuantiFERON—TB Gold (QFT-Gold), an interferon-gamma release assay (IGRA). It has been shown that BCG-vaccinated individuals have an increased chance of testing positive with the TST even when no infection is present; therefore QFT-Gold testing was recommended to rule out the possibility of false-positive TSTs. QFT-Gold has been shown to classify BCG-vaccinated individuals more accurately than the TST, and as such is a useful method to confirm positive TST results in BCG-vaccinated populations.

Eleven out of twenty TST-positive contacts agreed to be retested with QFT-Gold. The testing was completed within a week. All eleven were successfully tested with QFT-Gold and all but one was negative. The only one that remained positive was from a male born in India, who also had other risk factors suggestive of past exposure. Therefore, by recognizing the shortcomings of the initial diagnostic modality in light of the target population and employing another method to confirm LTBI diagnosis in close contacts, recent transmission was ruled out and needless expansion of the investigation was avoided.

QuantiFERON (QFT) Background:

For the past one hundred years, the TST was the only test available for detection of latent tuberculosis infection.¹ However, this test cross-reacts with non-tuberculosis mycobacteria as well as the *Mycobacterium bovis* bacilli Calmette-Guérin (BCG) vaccine. The BCG vaccine has been widely used, often cited as the most frequently used vaccine in the world.

QuantiFERON-TB (QFT, Cellestis) is an enzyme-linked immunosorbant assay (ELISA) that was approved by the United States Food and Drug Administration (FDA) in 2001 for the detection of latent tuberculosis infection (LTBI) in adults.^{2, 3} It measures interferon-gamma (IFN- γ) release using synthetic proteins specific to *Mycobacterium tuberculosis* (along with a short list of other mycobacteria). QFT measures cellular immunity more directly and also includes a control (*Mycobacterium avium* protein derivative).² Additionally, QFT requires only

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one visit and is complete within 24 hours, whereas TST requires a follow-up reading 48-72 hours later. QFT is no longer commercially available.

QFT-Gold (Cellestis) is a newer IFN- γ -based ELISA and received FDA approval in May 2005 as an aid in diagnosing both LTBI and TB disease. It uses different antigens, different measurement methodology, and is interpreted differently than QFT. Direct comparison indicated a similar sensitivity between QFT-G and TST for detecting untreated culture-confirmed tuberculosis and after expert review CDC recommended that QFT-G may be used in all circumstances that TST is used.⁴

It is difficult to assess the accuracy of indirect tests for TB infection (e.g. TST and QFT-G) due to a lack of a "gold standard" (highly accurate) test for LTBI. Therefore any observed disagreement between the two tests is hard to interpret, as the differences could be due to inaccuracies in either (or both) tests. In the absence of a gold standard we rely on the accumulation of experiences with the tests, particularly in groups of patients with high probability of being either negative or positive, and on the identification of factors associated with test failure (e.g. prior BCG vaccination for TST).

In addition to QFT-Gold, two other interferon-gamma release assays are currently FDA approved and available: QuantiFERON-TB Gold In Tube and T-SPOT TB; however neither of these tests were used in the previous case.

Teaching Points:

- Tuberculin skin testing may give a false-positive reaction in patients who have previously received BCG vaccination, which is often the case in foreign-born individuals. The large discordance between TST and QFT-G results is almost entirely attributed to BCG vaccination status, in other words false-positive TST results.
- A more accurate test for tuberculosis can save time with problems arising during contact investigations, especially regarding foreign-born contacts that are more likely to have been BCG-vaccinated. In this case, without this information the nurse would have had to assume that the positive TSTs were recent transmission and felt compelled to needlessly expand the investigation.
- CDC recommends that QFT-GIT or Tspot TB can be used in any way TST is used, including contact investigations, evaluation of BCG-vaccinated recent immigrants, and TB screening of healthcare workers. A positive result should initiate the same medical and public health interventions as a positive TST result.⁴
- QFT-GIT or Tspot TB appears to be a very specific test for evaluation of persons with a history of BCG vaccination. False positive results have been reported in serial testing of health care workers. However, its sensitivity (chance of false negative) has been questioned³, in which case QFT may be less useful for ruling-out than for confirmation, especially when a patient has symptoms and risk factors consistent with TB disease. Indeterminate or falsely negative results are also more common in immunocompromised populations and young children. Most pediatric experts believe additional information is needed before substituting a blood based test for the TST, especially in children less than two years of age. For very young children there is a suggestion that the T Spot is more sensitive.
- The Heartland National TB Center has developed a product outlining testing guidelines for college campuses, including screening all incoming students for risk factors for tuberculosis based on the recommendations of the American College Health Association and the Centers for Disease Control and Prevention. International students coming from countries with a high incidence (>20/100,000) of TB disease should be tested by either method. This product provides guidance for utilizing QFT-G for campus-based TB screening and testing programs.

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FOOTNOTES:

1. Diel, R., et al., *Tuberculosis Contact Investigation with a New, Specific Blood Test in a Low-incidence Population Containing a High Proportion of BCG-vaccinated Persons*. Respiratory Research, 2006. 7(1): p. 77.
2. Nguyen, M., S. Perry, and J. Parsonnet, *QuantiFERON-TB Predicts Tuberculin Skin Test Boosting in US Foreign-born*. The International Journal of Tuberculosis and Lung Disease, 2005. 9: p. 985-991.
3. Dewan, P.K., J. Grinsdale, and L.M. Kawamura, *Low Sensitivity of a Whole-Blood Interferon- γ Release Assay for Detection of Active Tuberculosis*. Clinical Infectious Diseases, 2007. 44(1): p. 69-73.
4. *Guidelines for the Investigation of Contacts of persons with Infectious Tuberculosis*. CDC MMWR 2005; 54 (RR-15, 49-55).

REFERENCES:

Model Tuberculosis Prevention Program for College Campuses. Heartland National TB Center. 2006.

Guidelines for the Investigation of Contacts of persons with Infectious Tuberculosis. CDC MMWR 2005; 54 (RR-15).

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