Interferon-Gamma Release Assays

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KEYWORDS

• Latent tuberculosis infection • Interferon-gamma release assays • Tuberculosis
• Tuberculin skin test • QuantiFERON • T-SPOT

KEY POINTS

- Diagnosis of latent tuberculosis infection (LTBI) should be targeted toward individuals and groups with high risk of progression to active tuberculosis (TB). Low-risk populations should not be screened.
- Interferon-gamma release assays (IGRAs) perform as well or better than the tuberculin skin test (TST) in most targeted populations. IGRAs are preferred for bacille Calmette-Guérin (BCG)-vaccinated populations.
- A positive IGRA in a person at low risk for TB exposure should be confirmed with a repeat test or another method before recommending LTBI treatment.
- The choice of which IGRA to use is generally based on the costs and feasibility of performing the test.

INTRODUCTION

TB remains a major global health problem. Worldwide, there are an estimated 2 billion people infected with *Mycobacterium tuberculosis* and from this large reservoir approximately 8.6 million people develop TB each year.[1] A staggering 1.3 million people die from TB annually, including more than 300,000 with HIV infection. Although the rates of TB are declining at approximately 2% per year, HIV coinfection and the emergence of drug-resistant strains of *M tuberculosis* threaten to undermine global TB control.

Identification and treatment of LTBI can substantially reduce the risk of developing TB and is a major focus of TB control in the United States.[2] Identification of all persons with LTBI would require screening large numbers of low-risk individuals that would not be cost-effective and would result in many false-positive test results.[3] Instead, the Centers for Disease Control and Prevention (CDC) recommends targeted testing in order to identify persons with LTBI who are at greater risk of progressing to TB and who

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Clin Lab Med 34 (2014) 337–349
http://dx.doi.org/10.1016/j.cll.2014.02.007 **labmed.theclinics.com**

would benefit from treatment of LTBI.[2] Persons with increased risk for developing TB include those who have been recently infected with *M tuberculosis* and those who have medical conditions that are associated with an increased risk of developing TB.

For nearly a century, the TST has been used to identify persons with TB infection. The TST is performed by the intradermal injection of purified protein derivative (PPD) that contains more than 200 proteins.[4] With such a diverse collection of antigens, it is not surprising that the TST lacks sensitivity and specificity, resulting in false-positive and false-negative test results. The 2 most important causes of false-positive results are infection with nontuberculous mycobacteria (NTM) and prior BCG vaccination. IGRAs are in vitro blood tests that measure the production of interferon gamma after stimulation with more specific mycobacterial antigens.[5] Because these antigens are not contained within BCG strains or most NTM, they provide a more specific test than the TST. This review focuses on IGRAs and their strengths and limitations for screening for LTBI.

MICROBIOLOGY

The genus *Mycobacterium* consists of slow-growing organisms that are widely distributed throughout the world and range from organisms that cause no human disease to those like *M tuberculosis* and *M leprae* that cause enormous morbidity and mortality.[6] TB is caused by members of the *M tuberculosis* complex that includes the clinically relevant species *M tuberculosis*, *M bovis*, and *M africanum.* All members of the *M tuberculosis* complex, except BCG substrains, contain a region of the genome referred to as the deleted region 1 (RD1); this region distinguishes virulent strains of *M bovis* from all BCG strains and is thought to represent part of the original attenuation during 1908–1921.[7] Within RD1 are genes that encode for the antigens, early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10); these antigens are more specific than PPD for *M tuberculosis* and are absent from all available strains of *M bovis* BCG.[8]

NTM refer to nonlepromatous organisms that are not members of the *M tuberculosis* complex.[6] NTM have been referred to as mycobacteria other than TB, atypical mycobacteria, and environmental mycobacteria. The latter designation refers to their widespread presence in the environment. NTM have several features that distinguish them from *M tuberculosis.* They have a wide range of pathogenicity, are not always associated with disease, and, unlike *M tuberculosis*, are not transmissible from human to human. Importantly, the incidence of NTM disease is increasing in many areas of the world, and the cause for this increase is unknown.[9] NTM share many antigens with *M tuberculosis* and thus can result in a false-positive TST result. Most strains of NTM, however, except *M marinum*, *M kansasii*, *M szulgai*, and *M flavescens*, do not encode for the antigens ESAT-6 and CFP-10, so they do not affect the results of IGRAs.[10]

EPIDEMIOLOGY

Understanding the epidemiology of TB is necessary to develop successful TB control interventions. As discussed previously, there were an estimated 8.6 million people who developed TB in 2012.[1] Twenty-two high-burden countries accounted for 81% of all estimated incident cases worldwide, with rates of approximately 150 to 300 cases per 100,000 population. In these high-burden countries, stopping transmission through TB case detection and treatment is the most important TB control intervention.