Review Article

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Latent tuberculosis infection is still a big challenge for tuberculosis control

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ABSTRACT

"Latent tuberculosis infection (LTBI) is a common worldwide infection. It involves about one third of people globally. It is defined as the presence of viable, but metabolically inactive *mycobacterium tuberculosis* bacilli, in a patient without symptoms and signs of active disease. LTBI is not contagious to others; however, it can be reactivated into an active disease in the future especially in the presence of any condition that impairs immunity of the patient. Detection and proper treatment of LTBI is vital in preventing reactivation especially in developed countries. Reactivation is considered as the most common cause of active tuberculosis.

Diagnosis of LTBI is made by tuberculin skin test (TST) and interferon gamma release assays (IGRAs). Both can be used but IGRAs is more specific, but more costly. Isoniazid (INH) monotherapy for 6 or 9 months can be used effectively in the treatment of LTBI."

Key Words: Latent tuberculosis infection, active tuberculosis, isoniazid, rifampicin

Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active tuberculosis (TB).[1] In latent tuberculosis infection (LTBI) viable Mycobacterium tuberculosis (MTB) bacilli are present in an individual but symptoms and signs of active disease are lacking, and the bacilli are relatively inactive metabolically.[2]

The only sign of latent tuberculosis infection is a positive reaction to the tuberculin skin test (TST) or TB blood tests.[3]

LTBI remains one of the most prevalent infectious conditions affecting humankind. It is estimated that roughly one third of the global population is infected.[4] Most of the cases are in developing countries. In a study done in the USA, more than 11 million person 4.2 % of the individual had LTBI as assessed by tuberculin skin

Table 1: Facts to be remembered about latent tuberculosis infection (LTBI)

1	It is TB infection not merely exposure.
2	It is not TB disease or active TB.
3	It is not contagious to others.
4	Has TB bacteria in his/her body that are alive but inactive.
5	Patient is completely asymptomatic has a normal chest x-ray and a negative sputum test.
6	It needs treatment to prevent transformation to an active disease especially in developed countries.
7	Usually has a skin test or blood test result indicating TB infection.
8	It is the huge part of the global TB iceberg.

Table 2: high risk group for transformation into an active TB disease
• Recent skin test converters (within the past 2 years)
• Young children. (Infants have a 40% chance of progressing to active disease and children are more likely to develop life-threatening forms of TB).
• Immigrants from countries with high rates of TB to developed countries (in the first 5 years of immigration)
• People with the following clinical conditions:
1. HIV/AIDS (10% annual risk of developing active TB)
2. Diabetes mellitus
3. Underweight (more than 10% below normal)
4. Chronic kidney disease especially haemodialysis patients
5. Gastrectomy or jejunoilial bypass
6. Silicosis
7. Head and neck cancer
8. Solid organ transplant recipients
9. Prolonged use of immunosuppressive drugs (prednisone 15 mg/day > 1 month and TNF-alpha antagonists)
10. Leukaemia or lymphoma
11. Chest X-rays with evidence of prior TB
12. Injection drug users

test.[2]

LTBI, unlike active tuberculosis, is not infectious and cannot spread mycobacterium bacilli to others (Table 1);[3] however, LTBI is not a benign disease. It possesses a major public health problem by its potential capability to be transferred into an active disease during the life especially when immunity compromises. What complicates the issue is that we cannot predict for sure who will develop active disease in the future and who will not; anyhow, immune compromised state is well recognized as a major risk factor for this transformation. Reports have stated that most cases of active tuberculosis result from reactivation of latent TB rather than new infection. Treatment of LTBI is designed to prevent (soon, or in the distant future) this progression from asymptomatic infection to symptomatic, potentially lethal and contagious active disease.[2] Identification and effective treatment of latent tuberculosis infection can reduce the risk of development of culture positive tuberculosis by 93 percent.[5]

Without treatment, about 5 to 10% of persons with LTBI will develop TB disease at some time in their lives. About half of those people will do so within the first two years of infection and about 0.1% per year thereafter.[3] For persons whose immune system is weak, especially those with HIV infection, the risk of developing TB disease is considerably higher than for persons with normal immune system. Advancing age, using drugs that suppress immunity, more exposure to diseases of low immunity, and more prevalence of chronic debilitating diseases are other factors that may be associated with increasing conversion rate. Persons with diabetes may have an 18% chance of converting to active tuberculosis. Persons with HIV and latent tuberculosis have a 10% chance of developing active tuberculosis every year.[6] (Table 2)

Tuberculosis including LTBI is transmitted through airborne spread of Mycobacterium tuberculosis. When a person with an active pulmonary TB coughs, aerosolized droplets containing bacilli can invade the lungs of close contacts. In 90-95% of cases, the infected person's immune system halts growth of the bacteria and active disease does not develop. The only change which can be seen at this stage is the conversion of TST or serological testing for TB into positive result. This conversion may take 8-10 weeks from time of exposure to occur and generally remains positive for life.

DIAGNOSIS

The goal of testing for latent tuberculosis

Table 3: Tuberculin skin test (TST) by Mantoux Technique
Use of purified protein derivative (PPD).
Inject PPD intradermally in the inner surface of the forearm.
Measure the result after 48-72 hours. Results are inaccurate if the result is measure more than 72 hours.
Measure the millimetres of induration not the erythema
Interpret according to complex algorithm incorporating TB risk factors and size of induration see table 4

Table 4: interpretation of TST
Five mm or more is positive in:
• HIV-positive person • Recent contacts of active tuberculosis cases • Persons with fibrotic changes on chest radiograph consistent with prior TB • Organ transplant recipients and other immunosuppressed patients who are on cytotoxic immune-suppressive agents such as cyclophosphamide or methotrexate. • Patients on long term systemic corticosteroid therapy (> than 4 weeks) and those on a dose of prednisone ≥ 15 mg/day or equivalent. • End stage renal disease.
Ten mm or more is positive in:
• Recent immigrants (< 5 years) from high-prevalence countries. • Injection drug users. • Residents and employees of high-risk congregate settings (e.g., prisons, nursing homes, hospitals, homeless shelters, etc.) • Mycobacteriology laboratory personnel. • Persons with clinical conditions that place them at high risk (e.g., diabetes, prolonged corticosteroid therapy, leukaemia, end-stage renal disease, chronic malabsorption syndromes, low body weight, etc.) • Children less than four years of age, or children and adolescents exposed to adults in high-risk categories • Infants, children, and adolescents exposed to adults in high-risk categories
Fifteen mm or more is positive in:
• Persons with no known risk factors for TB. Reactions larger than 15 mm are unlikely to be due to previous BCG vaccination or exposure to environmental mycobacteria.

infection is to identify individuals who are at increased risk for the development of tuberculosis and therefore would benefit from treatment of latent TB infection.[7, 8]

There are two main tests for the identification of LTBI: (1) ***Tuberculin skin test*** (TST) and (2) ***Interferon gamma release assays*** (IGRAs). Both are indirect, in that they evaluate the presence of host cell–mediated immunity rather than detect actual mycobacterial organisms or antigens. As such, neither can distinguish active disease from latent infection so it is discouraged to use these tests for the diagnosis of active tuberculosis. Both tests have limitations as they cannot distinguish between latent infection with viable microorganisms and healed/treated infections; they also poorly predict who will progress into an active TB.[1]

Diagnosis is used for two groups. The *first-group* is identification of new infections in those who have close contact with active pulmonary tuberculosis. The younger the age of the exposed person the more is the risk to have the infection. The test should be repeated 8-10 weeks after exposure if the first test is negative. The *second group* is to do the test to detect those who have increased risk of reactivation. In those group the test can be done once, and no need to repeat it again.

Tuberculin skin test: Is the oldest test used (table 3). The interpretation of the results depends on transverse diameter of an induration and the patient's associated co-morbidities and the presence of susceptibility to get active infection.[3] (Table 4) Sensitivity is 98 percent using the 5 mm cutoff point, 90 percent using the 10 mm cutoff point, but only 50 to 60 percent using the 15 mm cutoff point.[9] The specificity of the

Table 5 : causes of false negative and false positive results of TST

False-positive result

- Infection with non tuberculous mycobacteria
- Previous BCG vaccination
- Incorrect method of TST administration
- Incorrect interpretation of reaction

False-negative result

- Cutaneous anergy (anergy is the inability to react to skin tests because of a weakened immune system)
- Recent TB infection (within 8-10 weeks of exposure)
- Very old TB infection (many years)
- Very young age (less than six months old)
- Recent live-virus vaccination (e.g., measles and smallpox)
- Overwhelming TB disease
- Some viral illnesses (e.g., measles and chicken pox)
- Incorrect method of TST administration
- Incorrect interpretation of reaction, insufficient dose and inadvertent subcutaneous injection.

test increases when cutoff point of induration in millimetres set at a higher level. The test has many false positive and false negative factors.[10, 11] (table 5)*

Interferon gamma release assays (IGRAs): These blood test detects the presence of Mycobacterium tuberculosis (TB) infection by measuring interferon-gamma (IFN-G) harvested in plasma from whole blood incubated with the M. tuberculosis-specific antigens. Two major types: The QuantiFERON-TB Gold are whole-blood based enzyme-linked immunosorbent assays (ELISAs) measuring the amount of IFN-γ produced in response to three M. tuberculosis antigens. In contrast, the enzyme-linked immunospot (ELISPOT)-based T-SPOT.TB (Oxford Immunotec, UK) measures the number of peripheral mononuclear cells that produce INF-γ after stimulation with ESAT-6 and CFP-10.

Both tests Rely on M. tuberculosis-specific antigens that are not present in BCG or most Nontuberculous mycobacteriums (NTMs),. Table 6 shows some of the WHO recommendations about these to tests.[12]

TREATMENT

INH preventive therapy was first formally recommended in the United States for persons with previously untreated TB or recent TST conversion in 1965.[13] Then these recommendations were expanded in 1967 to include persons under age 20 years and persons with specified medical conditions with a positive TST.[14]

The current available treatments have an efficacy ranging from 60-90 % in preventing reactivation of TB.[15] However, this potential benefit needs to be carefully balanced against the risk of drug-related adverse events. Risk of serious and potentially fatal adverse effects of drugs used, high cost of diagnosis and treatment, and presence of imperfect tests used so far preclude population-wide mass testing and treatment for LTBI.[16] Treatment of LTBI has only

Table 6: Recommendations of the WHO about the Interferon gamma release assays (IGRAs)

- There is insufficient data and low quality evidence on the performance of IGRAs in low- and middle-income countries, typically those with a high TB and/or HIV burden;
- IGRAs and the TST cannot accurately predict the risk of infected individuals developing active TB disease;
- Neither IGRAs nor the TST should be used for the diagnosis of active TB disease;
- IGRAs are more costly and technically complex to do than the TST. Given comparable performance but increased cost, replacing the TST by IGRAs as a public health intervention in resource-constrained settings is not recommended.

* In NTP in Iraq 10 mm is considered the cut off point in all patients

been demonstrated to be effective in those with a positive TST or IGRA. Several clinical trials have failed to demonstrate a benefit of treatment in immunocompromised individuals at risk but with a negative TST or IGRA.

Before we decide to treat a patient who shows positive TST or IGRA we should do the followings:

- ***Assess the likelihood that a positive TST or IGRA represents true TB infection.*** This is made by careful history and comprehensive physical examination. Chest radiography and sputum examination are needed to exclude active tuberculosis. By this we are not only detect active disease but also to avoid inadvertent monotherapy of active disease that could lead to resistance.
- ***Estimate the likelihood of progression to active TB if actually infected.*** by detecting the history of contact with active TB and presence of co-morbidities that render a person susceptible to reactivation. **Table 2**
- ***Evaluate the potential risks for adverse reactions to treatment.*** The main adverse effect of LTBI treatment is INH-related hepatotoxicity. The strongest predictor of hepatotoxicity is age. Those younger than 20 years old have less than a 0.1% chance of hepatotoxicity during LTBI treatment, whereas those over 65 years are exposed to a risk around 2% to 5%.

The important point deserves to be mentioned here is that LTBI is not an active disease and patient is usually asymptomatic so whenever a treatment regimen is introduced a considerable attention should be pied not only to its effectiveness but also to its adverse effect profile especially when some of these side effects are serious or even fatal like hepatotoxicity.

A meta-analysis has evaluated the efficacy and safety of treatment of LTBI in 53 studies.[17] Studies have used more than one regimen in the treatment of LTBI. All have compared the regimen used to placebo and none have directly compared one regimen to another. This meta-analysis stated that differences of INH monotherapy to other therapies is mild and therefore of limited statistical or clinical value. Four months of rifampicin (RMP) monotherapy, can also be used as LTBI regimen, ranked highly for both efficacy and a low hepatotoxicity profile in comparison with other treatments. This short duration of RMP monotherapy has been reported to be at least as effective as INH and has possibly higher rates of acceptance and completion.[18] Regimens containing pyrazinamide (PZA) were found to be efficacious but generally had unacceptable toxicity. Cost and availability of INH make it more preferable drug to treat LTBI in developing countries.

WHO has recommended in resources constrained 6 months monotherapy with INH. The Centers for Disease Control and Prevention also advises that INH be administered for 6 or 9 months. [19] the 9 months regimen is more efficacious but 6 months treatment may be more cost-effective and result in greater adherence by patients. Contacts of INH-monoresistant cases can be offered 4 months of RIF daily.

WHO expert panel has showed that INH monotherapy fo 6 months, INH monotherapy for 9 months, rifampicin monotherapy for 3-4 months and rifampicin with INH for 3-4 months have the same efficacy. However, in terms of safety, a 3–4 months rifampicin regimen and a 3-month weekly rifapentine plus isoniazid regimen had fewer hepatotoxicity events compared to the 6-month and 9-month isoniazid regimen, respectively.[16]

Whatever the regimen used patient should be monitored at least monthly for clinical symptoms of hepatitis.

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Abbreviation list: Bacillus Calmette–Guérin (**BCG**), enzyme-linked immunosorbent assays (**ELISAs**), Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome (**HIV/AIDS**), interferon-gamma (**IFN-G**), Interferon Gamma Release Assays (**IGRAs**), Isoniazid (**INH**), Latent Tuberculosis Infection (**LTBI**), Mycobacterium tuberculosis (**MTB**), Nontuberculous mycobacteriums (**NTM**), Pyrazinamide (**PZA**), rifampicin (**RMP**), Tuberculin Skin Test (**TST**), Tuberculosis (**TB**)

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