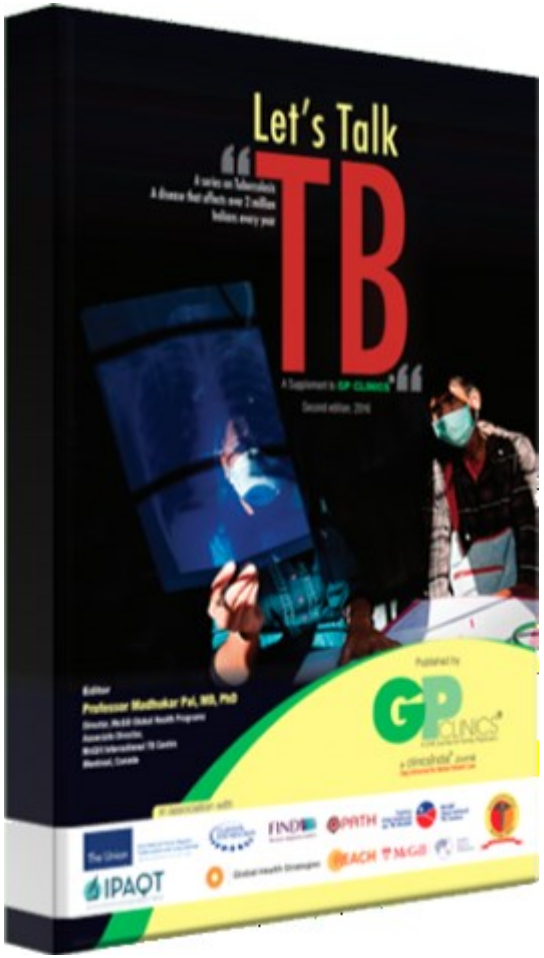

Let's Talk TB:

A Supplement to GP CLINICS

Chapter 7: Management of Latent Tuberculosis Infection

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Latent TB Infection

- Most individuals who get exposed to *Mycobacterium tuberculosis* (MTB) manage to eliminate or contain the infection using host T-cell immune defenses
- However, some MTB bacilli may remain viable (latent) and "reactivate" later to cause active TB disease
  - Latent TB Infection (LTBI)

LTBI is Asymptomatic

- Although LTBI and active TB disease are part of a dynamic spectrum, people with LTBI are asymptomatic and not infectious
- Nearly 50% of doctors and healthcare workers in India will test positive on the Mantoux tuberculin skin test
  - However, a majority will not display any TB symptoms, or develop active TB disease
    - Presumably, have LTBI

LTBI is Asymptomatic

- Some healthcare workers may go on to develop symptoms
- If active TB:
  - Require the standard 4-drug short course anti-TB therapy

Preventive Therapy

- Identification and treatment (i.e. preventive therapy or prophylaxis) of LTBI can substantially reduce the risk of development of active disease
  - By as much as 60%
  - An important TB control strategy in low-TB incidence settings where reactivation disease usually accounts for the majority of non-imported TB disease

LTBI Screening and Treatment

- LTBI screening and treatment is a major component of TB control programs in both USA and Canada
  - Large numbers of individuals are tested for LTBI and treated with isoniazid for 9 months
- However, LTBI screening and treatment is rarely done in high TB burden countries such as India
  - This is because nearly 40% of the population is estimated to have latent TB infection

Goal of Testing for LTBI

- The goal of testing for LTBI is to identify individuals who are at increased risk for the development of active TB
  - These individuals would benefit most from treatment of LTBI
- No diagnostic gold standard for LTBI and all existing tests are immunological tests that provide indirect evidence of sensitization of the host to TB antigens

Available Tests

- Two available tests for identification of LTBI:
  - Tuberculin skin test (TST)
  - Interferon-gamma release assays (IGRA)

TST

- TST is usually performed using the Mantoux skin test method (**Figure 1)**
- Purified protein derivative (PPD) is the antigen injected intradermally
- Skin induration is read after a period of 48 – 72 hours
  - In India, a 10 mm induration is considered positive.

Figure 1 – Tuberculin skin test being administered, using the Mantoux method.

IGRAs

- IGRAs are done *in vitro*
- Instead of PPD, they use highly specific peptides from two main antigens
  - Early secreted antigenic target (**ESAT6**)
  - Culture filtrate protein (**CFP10**)
- Commercial IGRAs include:
  - QuantiFERON-TB Gold In Tube (Qiagen, USA) (**Figure 2)**
  - T-SPOT.TB (Oxford Immunotec, UK)

Figure 2 – QuantiFERON TB Gold In Tube is an ELISA-based IGRA test for TB infection. It is not recommended for active TB detection.

TST and IGRA

- Both TST and IGRA depend on cell-mediated immunity (memory T-cell response), and a positive result suggests that the patient has been exposed and sensitized to MTB in the past

TST and IGRA

- Both represent indirect markers of MTB exposure and measure a cellular immune response to MTB
- Read as mm induration with the TST, and amount of interferon-gamma released by T-cells in IGRAs
- Neither test can accurately differentiate between LTBI and active TB
- Neither test can resolve the various stages within the spectrum of MTB infection

TST and IGRA

- Both TST and IGRA have reduced sensitivity in immunocompromised patients (e.g. people living with HIV/AIDS) and have low predictive value for progression to active TB
  - Majority of individuals with positive TST or IGRA results will not progress to active TB disease

RNTCP: Revised National TB Control Program

- Given the very high TB burden of active TB in India, it is not surprising that nearly 40% of Indians are estimated to be latently infected
- Given the large number of latently infected individuals in the country, the Revised National TB Control Program (RNTCP) does not give priority to LTBI detection and treatment in the public sector
- This is true for most high TB burden countries around the world

High Burden Countries

- For high burden countries like India, what should be the approach towards management of LTBI?
  - In 2014, WHO published its first comprehensive guideline on management of latent TB infection.
  - This guideline offers a clear, evidence-based algorithm (**Figure 3)**

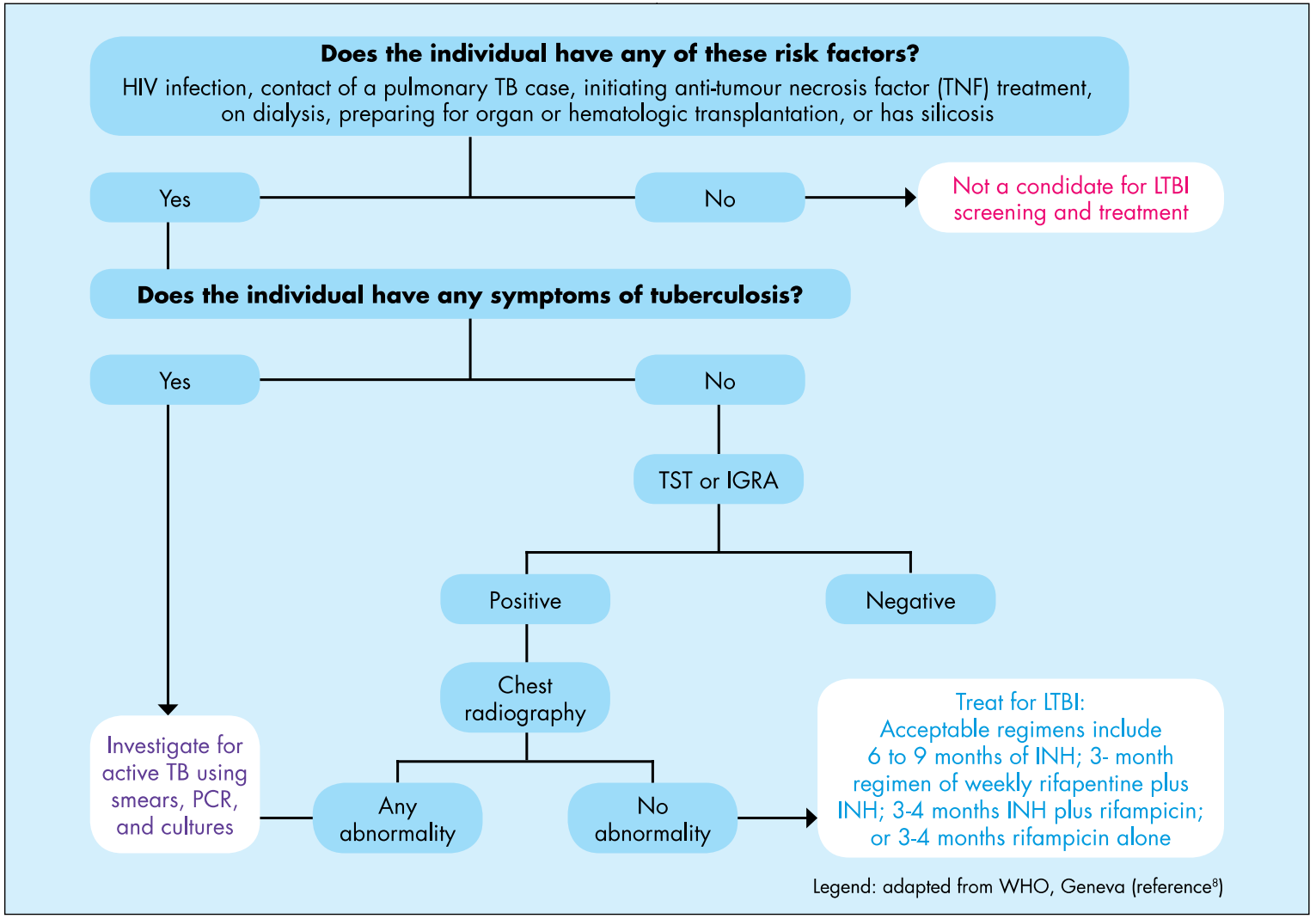

Figure 3 – WHO algorithm for latent TB infection management.

WHO Risk Groups

- As shown in the algorithm, WHO recommends that only selected risk groups should be evaluated for LTBI
- These include:
  - People living with HIV
  - Adult and child contacts of pulmonary TB cases
  - Patients initiating anti-tumour necrosis factor (TNF-alpha) treatment
  - Patients with end stage renal failure on dialysis
  - Patients preparing for organ or hematologic transplantation
  - Patients with silicosis
- The rationale for giving priority to these subgroups is that they are at very high risk of progressing from latent infection to active disease
  - This could be prevented by treating LTBI

WHO Risk Groups

- If an individual has any of the above risk factors, the WHO algorithm requires that they be assessed for TB symptoms
- If any TB symptom is present (e.g. cough, fever, weight loss, hemoptysis, night sweats) then the focus should be on diagnosing active TB using WHO and RNTCP-endorsed microbiological tests:
  - Smear microscopy
  - TB cultures
  - Molecular tests
    - Xpert MTB/RIF (GeneXpert, Cepheid Inc, USA)
    - Line probe assays: Genotype MTBDRplus (Hain LifeScience, Germany)

Chest X-Rays

- A chest x-ray can also be used as part of the work-up for active TB

No Symptoms?

- If the individual has no symptoms, then WHO recommends that either TST or an IGRA be used to test for LTBI in high-income and upper middle-income countries with estimated TB incidence less than 100 per 100000
- TST is preferred and IGRA should not replace TST in low-income and other middle-income countries

Ruling out the Active Disease

- If either TST or IGRA is positive, then the next step is to rule out active disease, before starting LTBI treatment
  - This is done by getting a chest x-ray
- If the x-ray shows any abnormalities, then it is critical to investigate for active TB
  - Using smear microscopy, TB cultures and molecular tests
- If the x-ray is normal, then the likelihood of active TB is very low
  - LTBI treatment can be initiated

LTBI Drug Regimens

- What are the drug regimens available for LTBI treatment?
  - Unlike active TB where 4 drugs are required in the intensive phase, the burden of bacteria in LTBI is quite low
  - Even a single TB drug is sufficient

LTBI Drug Regimens

- As shown in the WHO algorithm, treatment options recommended by WHO include:
- 6 to 9 months of isoniazid
- 3-month regimen of weekly rifapentine + isoniazid
  - or 3–4 months isoniazid + rifampicin
  - or 3–4 months rifampicin alone

LTBI Drug Regimens

- All regimens are known to be efficacious, but adherence can be poor with longer regimens:
  - Such as 9 months of isoniazid
- Rifampicin containing regimens may be more suitable in populations with a high background level of isoniazid mono-resistance

Table 1– Recommended drug dosages for acceptable LTBI treatment regimens

Drug regimen	Dose per body weight	Maximum dose
Daily **Isoniazid** alone for 6 or 9 months	Adults = 5mg/kg Children = 10 mg/kg	300 mg
Daily **Rifampicin** alone for 3-4 months	Adults = 10 mg/kg Children = 10 mg/kg	600 mg
Daily **Isoniazid** plus **Rifampicin** for 3-4 months	**Isoniazid** Adults = 5 mg/kg Children = 10 mg/kg **Rifampicin** Adults and children = 10 mg/kg	**Isoniazid** = 300 mg **Rifampicin** = 600 mg
Weekly **Rifapentine** plus **Isoniazid** for 3 months (12 doses)	Adults and children **Isoniazid:** 15 mg/kg **Rifapentine** (by body weight): 10.0-14.0 kg = 300 mg 14.1-25.0 kg = 450 mg 25.1-32.0 kg = 600 mg 32.1-49.9 kg = 750 mg	**Isoniazid** = 900 mg **Rifapentine** = 900 mg

Legend: adapted from WHO, Geneva (reference[8])

Counseling patients with LTBI

- Regardless of the regimen used for LTBI, it is important to ensure adherence, and provide patients adequate counseling about:
  - Why they are being treated for LTBI (despite not having symptoms)
  - Likely adverse events
  - Monthly follow-up visits
- The risk of toxicity is highest with isoniazid, especially in older individuals and those who consume alcohol

Concerns of Misuse

- In India, there is concern that tests such as Mantoux and IGRAs (e.g. TB Gold, TB Platinum) are being misused for active TB diagnosis
  - The WHO algorithm clearly shows that when doctors suspect active TB they should be testing for active TB
    - NOT screening for LTBI

Standards for TB Care in India (STCI)

- The **Standards for TB Care in India** (STCI) clearly states that both TST and IGRAs should not be used for the diagnosis of active TB in high endemic settings like India

Over-diagnosis of TB

- If IGRAs are used for active TB diagnosis, this will result in significant over-diagnosis of TB, because of the high background prevalence of LTBI in India

In Children

- In children, STCI suggests that the Mantoux test may have some value as a test for infection, in addition to chest x-rays, symptoms, history of contact, and other microbiological investigations
  - e.g. Gastric juice acid fast bacilli and Xpert MTB/RIF

Important Considerations

- LTBI screening must be restricted to specific high risk populations in India, where the benefits of LTBI treatment outweigh any risks
  - While either TST or IGRA can be used for LTBI screening, it is important to make sure that these tests are not used for active TB diagnosis

Important Considerations

- For persons with symptoms or abnormal chest x-rays, physicians should order smears, cultures, and molecular tests
  - These tests are now available in the public as well as the private sector in India
- If LTBI is diagnosed, then physicians must rule-out TB disease with chest x-rays before starting one of the recommended drug regimens
- It is important to ensure adherence, and provide adequate counseling to ensure that patients do not stop therapy prematurely

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