DIAGNOSING AND TREATING LATENT TUBERCULOSIS INFECTION (LTBI)

LEARNING OBJECTIVES

Upon completion of this session, participants will be able to:

1. Understand the advantages and disadvantages of the TST and IGRA
2. Recognize CDC population preferences in the use of the TST and IGRA
3. Describe current regimens for the treatment of LTBI

INDEX OF MATERIALS

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<td>Presented by: Gayle Schack, PHN, MS</td>
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SUPPLEMENTAL MATERIAL

None
ADDITIONAL REFERENCES


Objectives

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  - Describe current regimens for the treatment of LTBI
Current Terms and Definitions

- **High risk person** - person who is at high risk for progression to disease
- **Latent TB infection (LTBI)** - presence of M. tb organisms without symptoms or radiographic evidence of TB disease
- **Short Course Therapies** - durations shorter than current regimens and defined by valid clinical trial data*
- **Treatment of LTBI** - essential in controlling and eliminating TB in the U.S. as it substantially reduces the risk that TB infection will progress to TB disease.

*Dr. Claude Carbone of CHU Bichat, Paris, France

Review of Transmission and Pathogenesis

- Person to person transmission through the lungs to lymphatic system and bloodstream
- Chance of infection increases with
  - Higher concentration of bacteria
  - More time spent with infectious person
  - Environment where bacteria can easily survive
- Risk factors for progression to disease
  - Recently infected
  - Clinical conditions that increase risk
LTBI
Diagnosis and Treatment

TB Tests
Tuberculin Skin Test & Interferon Gamma Release Assay

Then
Now
Tuberculin Skin Test (TST)
- Detects cell-mediated immunity to \textit{Mtb} through a delayed-type hypersensitivity reaction using a protein fraction of heat-inactivated tubercle bacilli
- Has been the standard method of diagnosing LTBI since the 1930’s

Advantages of TST
- Easy to perform
- Low cost
- Observation (reading) reflects a polyclonal immune response
- Foundation of well controlled studies
- Well established definitions of TST conversion
Disadvantages of TST

- Need trained person to place and interpret test
- Inter- and intra-reader variability in interpretation
- 2 visits necessary
- Need 2 tests for baseline for serial testing
- False positives (i.e. BCG ad NTMs)
- False negatives (i.e. overwhelming disease, poor administration)

Administering the TST

- Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle
- Produce a wheal 6 to 10 mm in diameter
Reading the TST

- Measure reaction in 48 to 72 hours
- Measure induration, not erythema
- Record reaction in millimeters, not "negative" or "positive"
- Ensure trained health care professional measures and interprets the TST

Reading the TST (2)

- Positive TST reactions can be measured accurately for up to 7 days
- Negative reactions can be read accurately for only 72 hours
- Educate patient and family regarding significance of a positive TST result
TST Interpretation

<table>
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<th>≥ 5 mm</th>
<th>≥ 10 mm</th>
<th>≥ 15 mm</th>
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<tr>
<td>HIV Immunosuppression: • ≥ 15 mg/day prednisone X 1 month • TNF antagonist Recent contact to infectious TB case Abnormal CXR Organ transplant</td>
<td>Recent immigrant Living/working in high risk congregate setting Injection drug use Children &lt; 5 years Mycobacteriology lab personnel High risk medical condition: • Silicosis • Chronic renal failure</td>
<td>No risk</td>
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Factors That May Cause False-positive TST Reactions

- Nontuberculous mycobacteria
- BCG vaccination
  - Consider a positive TST result to indicate TB infection if risk factors are present (CDC)
Factors That May Cause False-negative TST Reactions

- Anergy
  - the inability to react to a TST because of a weakened immune system
- Recent TB infection
  - 2 to 10 weeks after exposure
- Very young age
  - newborns

Factors That May Cause False-negative TST Reactions (2)

- Live-virus vaccination
- measles or smallpox
- Overwhelming TB disease
- Poor TST administration technique
  - TST injection too shallow or too deep, or wheal too small, drawing up syringe and not administering immediately
Two-Step Testing

A strategy to determine the difference between boosted reactions and reactions due to recent infection.

- If first TST is positive, consider the person infected
- If first TST is negative, give second TST 1–3 weeks later
- If second TST is positive, consider the person infected
- If second TST is negative, consider the person uninfected at baseline

Two-Step Testing (2)

- Use two-step tests for initial baseline skin testing of adults who will be retested periodically (e.g., health care workers)
BCG and TST

- Tuberculin skin testing not contraindicated for BCG vaccinated persons
- Diagnosis and treatment for LTBI considered for any BCG vaccinated person whose TST is positive, especially if any of these circumstances are present:
  - Contact of another person with infectious TB
  - Born or resided in high TB prevalence country
  - Continually exposed to populations where TB prevalence is high

BCG Atlas

- Detailed information on current and past BCG policies and practices for over 180 countries
- Useful resource for clinicians, policymakers and researchers
- May be helpful for better interpretation of TB diagnostics as well as design of new TB vaccines
IGRAs

- Assays are primarily a reflection of a CD4 T-cell immune response to antigens
- Two IGRAs available:
  - QuantiFERON®-TB Gold In-Tube
    (Cellestis LTD, Victoria, Australia)
  - T-Spot.TB
    (Oxford Immunotec Ltd, Oxford, UK)

Advantages of IGRA’s

- BCG-vaccinated population
- Screening hard to reach populations
  - One patient visit
  - No need for 2-step testing
Disadvantages of IGRAs

- Requires blood draw
- Requires access to sophisticated lab
- Indeterminate rate may be higher in practice than in studies

IGRA Guidelines
ATS/IDSA/CDC

- Official American Thoracic Society/Infectious Disease Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children
- Published December 8, 2016
Persons 5 years and older

- Recommend IGRA rather than a TST in individuals 5 years and older who:
  - Are likely to be infected with \textit{Mtb} and
  - Have a \textbf{low or intermediate risk} of disease progression and
  - Decision made that testing is warranted and
  - Either have a history of BCG vaccination or are unlikely to return for TST reading

All Other Persons 5 years and Older

- Suggest IGRA rather than a TST in individuals 5 years and older who
  - are likely to be infected with \textit{Mtb} and
  - who have a \textbf{low or intermediate risk} of disease progression and
  - and it is decided that testing for LTBI is warranted
Preference for TST or IGRA

- Insufficient data to recommend a preference for either a TST or an IGRA as the 1st line diagnostic test in persons 5 years and older who
  - are likely to be infected with MTB and
  - who have a high risk of progression to disease and
  - a TB test is warranted

Persons at Low Risk

- Recommend NOT testing for Mtb*
- If done, suggest
  - IGRA instead of TST
  - 2nd test if the initial test is positive
    - IGRA or TST
    - Considered infected only if both tests are positive

*May be required by law or credentialing bodies
Children Under 5 years

- Suggest TST rather than and IGRA in
  - healthy children
  - It is warranted that a test for LTBI is needed

Boosting an IGRA

- Prior placement of a TST can boost an IGRA, particularly in those individuals who were already IGRA positive to begin with
- Can be observed in as little as 3 days post TST administration
- Boosting may wane after several months
- When dual testing collect IGRA first or concurrently to TST placement
Online TST/IGRA Interpreter

- Estimates the risk of active TB
- TST reaction of ≥5mm
- Based on person’s clinical profile
- Intended for adults tested with standard TST and/or IGRA
- http://www.tstin3d.com/

Treatment of Latent TB Infection (LTBI)
LTBI Diagnosis and Treatment

- Why treat?
  - TB remains a disease with a mortality rate of 7-9%
  - Treating LTBI can break the cycle of progression to TB and spread to new contacts

Initiating Treatment

- Before initiating treatment for LTBI:
  - Rule out TB disease
    - CXR
    - Sputum samples (wait for culture result if sputum samples obtained)
  - Determine prior history of treatment for LTBI or TB disease
  - Obtain HIV antibody test
  - Assess risks and benefits of treatment (e.g., medical history, medications, adverse effects)
Treatment of LTBI Options

- Short course regimens
  - 12 dose INH/rifapentine regimen (3hp)
  - 4 months rifapin

- INH regimens

12 INH/Rifapentine – 3hp

- 12 week INH and rifapentine once weekly by DOT
- Consider in persons
  - 2 years and older
  - Contacts
  - Radiographic findings of healed pulmonary TB
  - HIV infected persons NOT on antiretrovials
Rifampin Regimens

- Rifampin (RIF) daily for 4 months
- If RIF cannot be used (HIV-infected persons receiving antiretroviral agents), use rifabutin
- RIF and PZA for 2 months should generally not be given (risk of severe liver injury and death*).

*MMWR August 8, 2003; 52 (31): 735-739

INH Regimens

- 9-month regimen of Isoniazid (INH)
- 6-month regimen is less effective but may be used if unable to complete 9 months
- May be given daily or intermittently (twice weekly)
- Use directly observed therapy (DOT) for intermittent regimen
Completion of Treatment

- Count doses, not months
  - Short course regimens
    - 3 months INH/rifapentine – 11 doses within 16 weeks
    - RIF x 4 months -- 120 doses within 6 months
  - INH regimens
    - 9 months INH -- minimum of 270 doses within 12 months
    - 6 months INH -- 180 doses within 9 months

Clinical Monitoring

- Instruct patient to report signs or symptoms of adverse drug reactions
  - Rash
  - Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
  - Fatigue or weakness
  - Dark urine
  - Persistent numbness in hands or feet
Laboratory Monitoring

- Baseline liver function tests (AST, ALT, and bilirubin) are NOT necessary except for patients with the following risk factors:
  - HIV infection
  - History of liver disease
  - Alcoholism
  - Pregnancy or in early post-partum period
  - For 3hp - consider in older persons taking medications for chronic medical conditions

INH Liver Toxicity

- Asymptomatic LFT elevation (up to 3X normal) in up to 20% on INH
  - Resolves with continued treatment
- Stop INH if LFTs exceed
  - 3X normal and symptomatic
  - 5X normal and asymptomatic
- Age related incidence of symptomatic liver toxicity
  - <0.5% under age 35
  - 2% over age 50
Adverse Events

- Report severe side effects and adverse events to the TB Control Branch
- Report adverse events to the FDA MedWatch at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm

Other Considerations
HIV-infected Individuals

- Treat with 3 months of INH/rifapentine if not on antiretrovirals
- RIF is contraindicated if patient also being treated with certain antiretroviral drugs
- Treat with 9 months of INH
- Even if TST- or IGRA-negative, treat when person has had recent, prolonged exposure to infectious TB or ongoing risk for exposure

Pregnancy

- TST has no adverse effect on pregnant mother or fetus
- Test only if risk factors present
- If positive test, obtain CXR using shielding
- Consider treatment while pregnant if HIV infected or recent contact
- Supplementation with B6 is recommended
Breastfeeding

- May take INH
- Supplementation with B6 is recommended
- Amount of INH secreted in breast milk is inadequate for treatment of infants exposed to TB

LTBI and Drug Resistance

- If person exposed to known INH-resistant TB, treat with 4 months of RIF
- If person exposed to known MDR/XDR TB, consult an expert
Re-treatment of LTBI

- Re-infection may occur
- Consider
  - Severity of exposure
  - Health and of person
  - Willingness to complete treatment

Management of Patients Who Miss Doses

- Extend or re-start treatment if interruptions were frequent or prolonged enough to preclude completion
- When treatment has been interrupted for more than 2 months, patient should be examined to rule out TB disease
- Recommend and arrange for DOT as needed
Summary

- Choose appropriate test
- Always rule out TB disease before starting treatment for LTBI
  - Wait for culture results if sputum collected
- Consider best regimen for patient
- Encourage completion of therapy