Approach to Latent Tuberculosis Infection (LTBI)

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ADVANCES IN INFECTIOUS DISEASES

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Objectives:

1. List the main risks for TB infection and progression to active disease
2. Describe advantages and disadvantages of TST and IGRA in LTBI diagnosis
3. Discuss regimen options for LTBI treatment
4. Describe the follow-up, monitoring, and treatment completion for LTBI therapy

Which of the following groups is least likely to be infected with TB?

1. Homeless person in San Francisco
2. Person born in Mexico
3. US born elderly person (> 70 year old)
4. San Francisco resident with HIV infection
Targeted Testing

Persons at high risk for developing TB disease fall into 2 categories:
1. Recently infected

2. Clinical conditions that increase risk of progressing from LTBI to TB disease

Recent Infection
- TST or IGRA converters (within past 2 yrs)
  - Skin test conversion is an increase of ≥10 mm within a 2-year period
  - 4-5% risk developing active disease within first 1-2 years. Risk doubles in children < 4 years old
  - 40% progression to disease in infants < 12 months
- Close contacts to person with infectious TB
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, healthcare facilities)

Risk Factors for Progression
- HIV infection – greatest risk
- Radiographic evidence of old, untreated tuberculosis (> 2 cm²)
- Immunosuppression
  - Organ transplant, prednisone >15mg/d for more than 1 month, TNF-α inhibitors

Horsburgh NEJM 2004, Horsburgh NEJM 2011
Risk Factors for Progression (2)

- Diabetes – most common risk
- Chronic renal failure
- Silicosis
- Leukemia/lymphoma
- Head/neck cancer
- Malnutrition, weight loss >10% of ideal weight, gastric bypass surgery

Horsburgh NEJM 2004, Horsburgh NEJM 2011

Case 1 - 25 yr old female

Radiology reading: Fibrotic opacity in the right upper lobe with pleural thickening consistent with scarring from old TB

Case 1 - 25 yr old female (2)

- Asymptomatic
- TST = 16mm
- 3 months post-partum
- No other PMHx, HIV (-)
- Sputum AFB smear (-) x 3

Would you start her on LTBI treatment?
1. Yes
2. No

(ARS on next slide)
Case 1 - 25 yr old female (2)
Would you start her on LTBI treatment?
1. Yes
2. No

Case 1 - 25 yr old female (3)
All 3 sputa grew MTB!

Two months into treatment...

How do you place a Tuberculin Skin Test (TST)?

Performing a TST
- Inject 0.1 ml of 5 TU PPD intradermally on volar surface of lower arm using a 27-gauge needle
- Produce a wheal 6 to 10 mm in diameter
How do you read the TST?

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

TST for LTBI Diagnosis
Criteria for a Positive Reaction

<table>
<thead>
<tr>
<th>≥5 mm</th>
<th>≥10 mm</th>
<th>≥15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>Recent immigrants</td>
<td>No risk*</td>
</tr>
<tr>
<td>Contact to active TB case</td>
<td>High-risk medical conditions</td>
<td></td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>Injection drug users</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Children &lt; 4 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Healthcare Workers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Residents of jails/nursing homes, hospitals</td>
<td></td>
</tr>
</tbody>
</table>

*These persons should not be screened in the absence of an indication

What if the patient comes back late?

If the patient returns after 72 hours
- Read the test
- If the reaction is large enough to be considered positive, record the result and proceed with the evaluation (i.e. CXR)
- If there is a small reaction or no reaction, the test should be repeated
What about BCG Vaccination?

- BCG protects children from developing severe forms of TB but does not protect from infection
- Prior BCG is not a contraindication for a TST
- The TST is considered reliable for diagnosing LTBI if the BCG was given > 1 year prior
- Reactions due to BCG wane over time so the CDC recommends interpreting (+) tests the same as persons without BCG

The BCG World Atlas

http://www.bcgatlas.org/

TST: Sensitivity for Active TB

Diel, Chest April 2010 137(4): 952
Advantages of the TST

- Cheap
- Relatively easy to perform
- Extensive experience and clinical data correlating a (+) TST with the risk of progressing to active TB

Limitations of the TST

- Subjective interpretation
- Difficult to maintain proficiency
- Requires 2 visits
- Affected by prior BCG vaccination and NTM infection
- Only moderately sensitive for active TB
- Despite > 100 yrs of use, still no standard place for recording results in the medical record

Case 2 - 20 y/o student

- Born in India, in US for 4 years
- Required to get TB testing for college enrollment
- TST = 11 mm  CXR = normal
  "It's due to my BCG"
- Asks for a "blood test for TB"
- Quantiferon-Gold in Tube (QFT-G in Tube)
- Result = positive
  IFN-g release from TB agonist - Nil = 1.15 IU/ml
  Reference cut-off for positive result ≥0.35 IU/ml
What is the Quantiferon-Gold in Tube?
“Interferon-gamma Release Assays”

- Blood tests for detecting TB infection
- Uses ESAT-6 and CFP-10 as antigens, which are more specific for *M. tuberculosis* complex
- Require only 1 visit to get a result
- Less subject to reader bias and error

Lancet 2000;356:1099-104
Tuberculosis complex | Antigens | Environmental strains
--- | --- | ---
M tuberculosis | + | -
M africanum | + | -
M bovis | + | -
BCG autotaxin | - | -
gothenburg | - | -
marseille | - | -
tokyo | - | -
denish | - | -
glaso | - | -
monreal | - | -
pasteur | - | -

M abscessus | - | -
M exmu | - | -
M brandi | - | -
M lenti | - | -
M cholerae | - | -
M fortuitum | - | -
M gordonii | - | -
M intracellulare | - | -
M kansasi | + | +
M marinum | + | +
M oceaver | - | -
M scrofulaceum | - | -
M xenopi | - | -

IGRAs are preferred for:
1. BCG vaccinated
2. Groups with historically low return rates for TST readings

Case 2 - 20 y/o student (2)
- Born in India
- Required to get TB testing for college enrollment
- TST = 11 mm  CXR = normal
  “It’s due to my BCG”
- QFT positive (TB-nil = 1.15 IU/ml)
  “It’s boosting from the TST”
- Repeat QFT negative (TB-nil = 0.34 IU/ml)
  “Finally we agree”
Online TB Risk Calculator
http://www.tstin3d.com/

QFT-GIT: Sensitivity for Active TB, limited to developed countries

Diel, Chest April 2010 137(4): 952

T-SPOT.TB: Sensitivity for Active TB

Diel, Chest April 2010 137(4): 952
Adults and children from Low-Incidence Countries as a Surrogate for Uninfected

Pooled Specificity = 0.99 (0.98-1.00)

Diel, Chest April 2010 137(4): 952

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Case 3 - 43y/o female with RA (1)

- Born in Mexico, in the U.S. since ’01
- Prior BCG
- Meds: Methotrexate, Prednisone
- TST = 21mm

Would you check an IGRA?
1. Yes
2. No

(ARS on next slide)

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Case 3 - 43y/o female with RA (1)

Would you check an IGRA?
1. Yes
2. No
Case 3 - 43y/o female with RA (2)

- Clinician obtained a QFT-Gold
  - Result - Negative (TB-nil = 0.09 IU/ml)
- TB Clinic repeats TST = 27mm

Risk for infection
Risk for progression

I recommended latent TB treatment

Summary on IGRAs

- Improved specificity over TST
- More sensitive than the TST for active TB but not high enough to exclude TB in a symptomatic patient
- Are the preferred test in:
  - BCG vaccinated
  - Persons unlikely to get a TST completed
- More costly and requires the ability to get the blood to the lab in a timely way

TREATMENT FOR LTBI
Before Initiating Treatment for LTBI

- Rule out active TB
  - CXR on everyone
  - sputum collection if the CXR is abnormal or the person is symptomatic
- Determine prior history of treatment for LTBI or TB disease
- Assess risks of toxicity
- Determine current and previous drug therapy

If you collect sputum cultures, wait for the results before beginning LTBI therapy

Current Treatment for LTBI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>Max: 300 mg</td>
<td>Daily</td>
<td>9 months</td>
<td>Preferred for everyone Complete 270 doses within 12 months</td>
</tr>
<tr>
<td></td>
<td>Children/adolescents 10-15mg/kg</td>
<td></td>
<td></td>
<td>6 months “acceptable” for:</td>
</tr>
<tr>
<td></td>
<td>300 mg if over 20 kg</td>
<td></td>
<td></td>
<td>• Immunocompetent adults without scarring on CXR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Programs unable to deliver 9 months Complete 180 doses within 9 months</td>
</tr>
</tbody>
</table>

Alternative Treatments for LTBI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>Twice weekly</td>
<td>9 months</td>
<td>Directly observed therapy</td>
</tr>
<tr>
<td>INH</td>
<td>Twice weekly</td>
<td>6 months</td>
<td>DOT Immunocompetent</td>
</tr>
<tr>
<td>Rifampin (with or without INH)</td>
<td>Daily</td>
<td>4 months</td>
<td>Immunocompetent</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Daily</td>
<td>6 months</td>
<td>For children or immunocompromised</td>
</tr>
</tbody>
</table>
Rifampin vs INH

Treatment completion
- 78% Rifampin vs 60% INH
Grade 3/4 adverse events
- 7/418 (1.7%) Rifampin vs. 17 / 422 (4.0%) INH

Menzies Ann Int Med 2008; 149:689

Important Considerations with Rifampin

- Drug-Drug interactions
  - Rifampin is a potent inducer of enzymes in the cytochrome p450 system and can decrease the efficacy of many medicines included oral contraceptives, warfarin, methadone, phenytoin, others

The Future of LTBI Treatment?

CDC TB Trials Consortium (TBTC) – “Prevent TB” Study (Study 26)
- Randomized, prospective trial
  - INH 900mg and rifapentine 900mg weekly by DOT for 3 months (12 doses)
  - INH 300mg daily SAT for 9 months
- >8,000 adults and children at high risk for progression to TB disease
The Future of LTBI Treatment? (2)

- Results presented at the International Union meeting in Berlin, November 2010

- INH/RPT compared to INH
  - Equally efficacious
  - Less toxicity
  - Better treatment completion (81% vs 69%, p < 0.001)

LTBI Treatment: DOT v SAT

- Most LTBI treatment is given as self-administered therapy
- Directly Observed therapy (DOT or DOPT) is reserved for:
  - Intermittent LTBI regimen
  - Children (all those < 5 and school age if able)
  - Persons in a monitored setting – jail, hospital, nursing home
  - Anyone unlikely to complete SAT (e.g., homeless)

Baseline Labs

- HIV testing is recommended for contacts
- Baseline hepatic function tests only if:
  - Initial work-up suggests possible liver disorder
  - Pregnant or early post-partum (first 3 months)
  - HIV positive
  - History of chronic liver disease
  - Taking other meds with potential for liver toxicity
Clinical Monitoring (1)

Instruct patients to stop therapy immediately and call if they develop:
- Nausea, vomiting, loss of appetite
- Right upper quadrant abdominal pain
- Jaundice
- Rash

Clinical Monitoring (2)

Other common side effects — these may be manageable without requiring discontinuation if laboratory tests normal:
- Fatigue
- Weakness
- Headache
- Numbness and tingling of the hands or feet (generally can be treated with Vitamin B6)

INH Hepatotoxicity

Reversible with early discontinuation
- Transaminitis 20%
- Clinical Hepatitis 0.1-0.15%
- Fatal Hepatitis <0.023%

Recommended to STOP therapy if:
1. AST or ALT >3 times normal (~110-120) and patient is symptomatic
   or
2. AST or ALT >5 times normal (~180 – 200)
Laboratory Monitoring

Repeat laboratory monitoring if patient has:

- Abnormal baseline results
- High risk for adverse reactions (e.g., HIV, Hep B/C)
- Taking other meds with potential for liver toxicity
- Symptoms of adverse reaction
- Recent pregnancy
- Liver enlargement or tenderness during examination

Follow-up

Monthly visits to:

- Address side effects
- Monitor for symptoms of active disease
- Establish rapport and encourage compliance
- Refill medications
- Check labs if needed