Basics of LTBI

“Doctor I feel fine...”
Treating Latent TB Infection in your practice
June 22nd, 2019

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DISCLOSURES

• I have no disclosures or conflicts of interest to report
Objectives

• Understand tests used for diagnosing LTBI and their limitations

• Understand advantages/disadvantages of current treatment options for LTBI

• Understand evidence supporting treatment of latent TB infection (LTBI)

Patient with Preventable TB

• 28 year old woman, originally from Mexico, presented to her primary care provider 5 years ago essentially for well visit

• Went back to PCP 5 years later:
  • Cough for 2 months, wheezing noted on exam
  • Inhaler offered, PFTs scheduled

• Urgent care visit 3 days after that visit
  • Continued cough, CXR obtained...
“atypical pneumonia”: azithromycin for 5 days

Patient with Preventable TB

- 5 months later: repeat PCP visit:
  - continued cough, no relief with albuterol
  - 8 lb. weight loss: BMI 18.6.
- QVAR and Claritin were added to her albuterol.
- Chest radiograph findings were noted → referred to pulmonary, CT chest ordered.
Patient with Preventable TB

- One month later: seen in the ED
  - continued chronic cough, tachycardic to 115. Was discharged
- Two days after ED visit in pulmonary clinic:
  - Working diagnosis of possible bronchiolitis, bronchoscopy planned but she didn’t have the funds to cover to copay

Patient with Preventable TB

- 3 weeks after pulm visit, 7 months into her illness
  - Went to the ED with headache for 7 days, fever, nausea/vomiting and body aches and sore throat
    - DX→ strep throat
    - RX→ azithromycin
    - Chest x-ray was noted to have “no acute findings.”
  - Went back twice in one week: persistent headaches, nausea vomiting and now photophobia, visual disturbances
    - DX→ tension headache
    - RX→ follow up with her primary care provider
Two days later, 8 months into her illness: family took her to another hospital
  - Somnolence, confusion
  - Continued nausea/vomiting
9/6: MRI/brain: diffuse focal flair hyperintensity; diffuse leptomeningeal enhancement compatible with meningitis.
LP: WBC 149, t prot 152, glucose 14
  - M. tuberculosis PCR positive

Bronchoalveolar lavage, smear positive for AFB and subsequently was identified to be Mycobacterium tuberculosis.
Additional studies:
  – QuantiFERON positive
  – HIV negative
Her hospital course was further notable for the development of seizures.
Started on TB treatment with isoniazid, rifampin, pyrazinamide and ethambutol and steroids due to meningitis.
Profoundly debilitated/confused and unable to care for herself at discharge
A review of how to identify individuals at risk for TB infection
Use this tool to identify asymptomatic adults for latent TB infection (LTBI) testing.
- Do not repeat testing unless there are new risk factors since the last test.
- Do not treat for LTBI until active TB disease has been excluded.

TST—how it works

Measurement of induration and erythema

Presentation of mycobacterial antigens

Antigen presenting cell

Memory T cell

Skin test

in-vitro blood test

Measurement of IFN-γ production

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Tuberculin Skin Testing
Mantoux Method

5 TU of PPD

48 to 72 hours

Interpretation depends on person's risk factors

Tuberculin Skin Test
Criteria for a Positive Reaction

<table>
<thead>
<tr>
<th>&gt;=5mm</th>
<th>&gt;=10mm</th>
<th>&gt;=15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positive</td>
<td>prior BCG vaccination</td>
<td>no risk</td>
</tr>
<tr>
<td>contacts</td>
<td>prior residence in a TB endemic area</td>
<td></td>
</tr>
<tr>
<td>abnormal chest radiograph</td>
<td>injection drug use</td>
<td></td>
</tr>
<tr>
<td>immunosuppression</td>
<td></td>
<td>children</td>
</tr>
<tr>
<td></td>
<td></td>
<td>congregate settings such as correctional facilities, nursing facilities, hospitals</td>
</tr>
</tbody>
</table>

Note: Skin test conversion is an increase of ≥10 mm to ≥ 10 mm within a 2-year period
**Tuberculin skin test interpretation:**

**False-negative results**

- **Host factors**
  - Immunosuppression
  - Recent TB infection (<3 months)
  - Age (newborn, elderly)
  - Infections (viral, fungal, bacterial)
  - Live virus vaccination
  - Overwhelming tuberculosis
  - ESRD
  - Other illness affecting lymphoid organs

- **Technical factors**
  - Tuberculin product (improper storage, contamination)
  - Improper method of administration, reading and/or recording of results


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**Tuberculin skin test interpretation:**

**False-positive results**

- Cross-reactions from atypical mycobacterial infections
- Recent or multiple BCG vaccination
- Misinterpretation of immediate hypersensitivity to tuberculin
- Switching tuberculin products (aplisol > tubersol)

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Antigens used in IGRAs compared to PPD

- M. tuberculosis antigens shared with NTM, & BCG
- Antigens specific to M. tuberculosis, e.g., ESAT-6 & CFP-10

Slide courtesy of Dr. David Horne

Ganguly et al, 2008: 88, 510-517

TST and QFT Specificity

<table>
<thead>
<tr>
<th></th>
<th>Specificity</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST without BCG</td>
<td>97</td>
<td>95–99</td>
</tr>
<tr>
<td>TST with BCG</td>
<td>59</td>
<td>46–73</td>
</tr>
<tr>
<td>QFT</td>
<td>96</td>
<td>94–98</td>
</tr>
</tbody>
</table>

Slide courtesy of Dr. Neha Shah


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QuantiFERON-Gold Plus (QFT-plus)

QFT-plus: interpreting the results

Interpretation of results

Results of the QFT-PLUS assay are interpreted objectively using QuantiFERON-TB Gold Plus analysis software.

- **M. tuberculosis infection is likely**
  - Nil ≤ 8.0; and
  - TB1 and/or TB2 minus Nil ≥ 0.35 and > 25% of Nil

- **M. tuberculosis infection is NOT likely**
  - Nil ≤ 8.0, Mitogen minus Nil ≥ 0.5; and
  - TB1 and TB2 minus Nil < 0.35 or ≥ 0.35 and < 25% of Nil

- **Likelihood of M. tuberculosis infection cannot be determined**
  - Nil > 8.0
  - Nil ≤ 8.0 and TB1 and TB2 < 0.35 or ≥ 0.35 and < 25% of Nil and Mitogen minus Nil < 0.5
T-SPOT Interpretation

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
<th>Borderline</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 8 spots*</td>
<td>≤ 4 spots*</td>
<td>5-7 spots*</td>
<td>Controls fail:</td>
</tr>
</tbody>
</table>

- High Nil
- Poor Mitogen response

* (TB Ag - Nil) and assumes appropriate control responses

IGRAs – Basic similarities

- Single blood draw
- Incubate blood cells with antigens from the region of difference 1 (RD1)
  - not contained in BCG but present in *M. bovis*
  - Antigens present in *M. marinum, kansasii, szulgai, and flavescens*
- Results available in 1 day
Indeterminate/borderline results

- Cannot determine whether someone has TB infection
  - Low lymphocyte count
  - Low lymphocyte activation potential
  - Specimen collection errors

- Repeat test with valid result (pos/neg) in 68% (Banach IJTLD 2011)
  - Repeating the test is often the next step

IGRA Screening & Low LTBI Risk

- IGRA responses may change over time
  - 2400 U.S. HCW, serial TST, QFT, T-SPOT (Dorman AJRCCM 2014)
  - Conversions occurred: TST 0.9%    QFT 6.1%    T-SPOT 8.3%
Can IGRAs be used to monitor a response to treatment?

- 15 studies that evaluated LTBI responses
- No consistent pattern using reversions or quantitative IFN-gamma levels

IGRA vs. TST

**Advantages** over TST
- Not affected by BCG vaccination
- Not affected by most non-tuberculous mycobacteria
- Interpretation is more objective
- No return visit needed for interpretation of test
- Patients and providers may lack confidence in TST results

**Disadvantages** over TST
- Blood draw
- Cost

Perform chest radiograph and consider repeating symptom screen. Are either abnormal?

If risk factors present, perform symptom screen. Symptom screen positive?

No further intervention

Evaluate for active TB/refer to public health

Yes

No

No

Yes

Perform IGRA or TST. Positive?

LTBI Treatment: Key considerations

Efficacy
- Ability to prevent disease among individuals adhering to medication

Effectiveness (adherence)
- Ability to prevent disease when used in public health practice

Drug interactions & adverse events

Monitoring requirements, cost, availability

Offer LTBI therapy if risk of developing active TB is >3% by the age of 80 or >0.1% annually: (http://www.tstin3d.com/)
Options:
1) Rifampin 10mg/kg max dose 600mg daily x 4 months. Review drug interactions.
2) Isoniazid/rifapentine once weekly for 12 doses. Review drug interactions.
3) INH 5mg/kg max dose 300mg daily with 25mg B6 x 9 months.
847 adults with LTBI in Canada, Brazil & Saudi Arabia

Randomized to:
- 4 months RIF (n=420)
- 9 months INH (n=424)

4 months
10mg/kg = 600mg daily unless underweight

Self-administered rifampin: better adherence than INH

Menzies D, Ann Intern Med 2008; 149:689

Inhibits RNA synthesis
Potent activity against slow-growing MTB

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Self-administered Rifampin

• Adverse effects
  • Dyspepsia
  • Orange discoloration to body fluids
  • Rash
  • Thrombocytopenia
  • Rare: neutropenia, hemolytic anemia, thrombocytopenia

• Drug interactions
  • Hormonal anti-contraceptives
  • Coumadin
  • Thyroid hormone
  • Anti-seizure agents
  • Antihypertensives
  • Antipsychotics
  • Plus many more

Rifampin—monitoring

• Check baseline labs if:
  ▪ HIV-positive
  ▪ History of liver disease
  ▪ Regular alcohol use
  ▪ Age >50
  ▪ Pregnant or post-partum (within 3 months)
  ▪ On hepatotoxic medications

• Labs during follow-up only if baseline labs elevated or symptomatic
• Monthly follow-up recommended
Isoniazid and Rifapentine both once weekly for 12 doses

- **Isoniazid:** 15 mg/kg, rounded up to the nearest 50 or 100 mg; 900 mg maximum
- **Rifapentine**
  - 10 to 14 kg: 300 mg
  - 14.1 to 25 kg: 450 mg
  - 25.1 to 32 kg: 600 mg
  - 32.1 to 49.9 kg: 750 mg
  - >50 kg: 900 mg maximum

- **Obtain LFTs:**
  - if aged >35
  - has underlying liver disease
  - pregnant/or within 3 months post-partum
  - Regular EtOH consumption or taking other hepatotoxic agents

Isoniazid with rifapentine

- **Adverse effects**
  - Dyspepsia
  - Nausea/vomiting
  - Fatigue
  - Flu-like illness
  - Headaches
  - Hepatotoxicity
  - rash

- **Drug interactions—some overlap with rifampin**
  - Hormonal anti-contraceptives
  - Coumadin
  - Antihypertensives
  - antiretrovirals
Isoniazid Regimens

Preferred
• INH daily for 9 months

Acceptable Alternatives
• INH twice/week for 9 months by DOT
• INH daily for 6 months
• INH twice/week for 6 months by DOT

Isoniazid: monitoring

• Check baseline labs if:
  ▪ HIV-positive
  ▪ History of liver disease
  ▪ Regular alcohol use
  ▪ Age >35
  ▪ Pregnant or post-partum (within 3 months)
  ▪ H/o injection drug use
  ▪ On hepatotoxic medications

• Labs during follow-up only if baseline labs elevated or symptomatic

• Monthly follow-up recommended
INH ADVERSE EVENTS

- Neurologic - interference in vitamin B₆ absorption
  - Higher risk in DM, renal insufficiency, alcoholism, malnutrition, HIV, pregnancy, seizure disorder
- GI
  - Hepatotoxicity
  - Nausea/vomiting
- Skin rash
- Drug interactions—always check!

Offer B6 at 25-50mg daily to individuals at higher risk for peripheral neuropathy

Summary Efficacy & Completion

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Efficacy</th>
<th>Mean completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months INH</td>
<td>90-92%</td>
<td>53-63%</td>
</tr>
<tr>
<td>6 months INH</td>
<td>41-76%</td>
<td>49-79%</td>
</tr>
<tr>
<td>4 months Rifampin</td>
<td>Equivalent to 9 months of INH</td>
<td>72-79%</td>
</tr>
<tr>
<td>3 months INH - Rifapentine</td>
<td>Equivalent to 9 months of INH</td>
<td>78%</td>
</tr>
</tbody>
</table>

Summary

• Neither an IGRA or TST can distinguish between latent TB infection and active TB
  • A negative test does not exclude active TB

• Test people at risk for infection
  • 1<sup>o</sup> people born or lived in a high-burden country
  • Prioritize those with risk for exposure AND progression (HIV, DM, ESRD etc.) on a programmatic level or clinic level to allow for scaling up of TB testing

Summary

• Treatment for LTBI should be discussed with all patients
  • Recommend only for those with significant risk of progression that outweighs the risk of adverse effects
  • Most experts would recommend LTBI treatment if lifetime risk is greater than 3-5%
Patient - follow up

• Completed 12 months of treatment

• Was able to make a complete recovery!