Tuberculosis in Primary Care

April 22, 2015
ADVANCES IN INFECTIOUS DISEASES

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Disclosure Slide

- I have nothing to disclose
Objectives:

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

We are not making progress toward TB elimination

Figure 1. TB Case Rates by Year 1990-2014
TB elimination model

What is the most significant barrier to testing/treating LTBI in your practice?

- Lack of time
- Unclear guidelines/lack TB knowledge
- Access to diagnostic testing (IGRAs)
- Lack of consistent documentation to track testing/treatment
Flowchart: Evaluation to Treatment of LTBI

At-risk person

TB test + symptom review

Negative

Positive

Chest x-ray

Normal

Abnormal

Treatment not indicated

Candidate for Rx of latent TB

Evaluate for active TB

Assess TB Risks First

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 $\geq 10$ 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 ~2X
- Smoking ~4X
- Chronic renal failure
- Silicosis
- Leukemia/lymphoma
- Head/neck cancer
- Malnutrition, weight loss >10% of ideal weight, gastric bypass surgery

Which of the following groups should be assessed annually for new TB exposure risk?

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
5. All of the above

Which of the following groups should be tested annually for 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
5. All of the above
What should be the frequency of re-testing for the following groups?

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

What should be the frequency of re-testing for the following groups? Assess risk annually – test if new risk

1. Homeless person in San Francisco (Annual)
2. Person born in Mexico (Known Contact or Travel)
3. US born elderly person (> 70 year old) (Known Contact or Travel)
4. San Francisco resident with HIV infection (Annual)
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...
Flowchart: Evaluation to Treatment of LTBI

At-risk person

TB test + symptom review

Negative

Treatment not indicated

Positive

Chest x-ray

Normal

Candidate for Rx of latent TB

Abnormal

Evaluate for active TB

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 (ie 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
QuantiFERON-Gold in tube

1. Collect 1mL of blood into K2-Antiicoagulant-EDTA tubes. Stir well. Incubate tubes at 37°C for 16-24 hrs.

2. Centrifuge tubes for 15 minutes.

3. Add conjugates, plasma samples and standards to ESA. Incubate for 50 minutes at room temperature.

4. Wash and add substrate. Read absorbance after 30 minutes.

5. Software calculates results and prints spots.

T-SPOT.TB

Collect peripheral venous blood → Centrifuge → Plasma PBMCs Red cells

Remove PBMCs, wash and count

Incubate overnight → Pre-coated wells

Add PBMCs and antigens to 4 wells

Wash, develop and dry plate → Count the coloured spots in each well
### Species Specificity of ESAT-6 and CFP-10

<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>ESAT</th>
<th>CFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>M tuberculosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M africanum</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M bovis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BCG substrain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gothenburg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>moreau</td>
<td>-</td>
<td>-</td>
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<tr>
<td>tice</td>
<td>-</td>
<td>-</td>
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<tr>
<td>tokyo</td>
<td>-</td>
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<tr>
<td>danish</td>
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</tr>
<tr>
<td>glaxo</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>montreal</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pasteur</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Environmental strains</th>
<th>ESAT</th>
<th>CFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>M abcessus</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M avium</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M branderi</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M celatum</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M cheloneae</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M fortuitoen</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M gordonii</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M intracellulare</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M kansasii</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M malmoense</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M marinum</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M oenavense</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M scrofulaceum</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M smegmatis</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M szulgai</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M terrae</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M vaccae</td>
<td>-</td>
<td>-</td>
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<tr>
<td>M xenopi</td>
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</tr>
</tbody>
</table>

### Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection — United States, 2010

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/
SF Guidelines for IGRAs

- BCG vaccinated (all ages, including pediatric)
- Unlikely to return for TST reading (homeless screening, mental health, substance use)
- Contact evaluation after TB exposure
- Maximize sensitivity for very immunocompromised populations (anti-TNF, organ transplant)

Indeterminate IGRAs

- Repeat test - most of the time, this will take care of the problem
- Reagent problem (Fall 2013)
  - Mitogen did not elicit typical immune response
  - If immune competent and known problem with reagent, if TB Ag-Nil < 0.35 IU, ok to clear
- Use alternate test (TST, other IGRA)
- If TB exposure risk, risk for progression, and indeterminate IGRA x 2, refer to specialist
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)
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

TST vs. IGRA - What to do with Discordant Results

- Avoid using two tests for TB screening
- TST(+)/IGRA(-)
  - Foreign born with BCG and no severe immunocompromising condition - attribute to BCG
  - Caveat - abnormal CXR confirmed old TB and with risk factor for progression to disease, consider treatment
  - U.S. born - with no risk factors for exposure or risk factors for progression - may be NTM colonization
- TST(-)/IGRA(+)
  - Foreign born with BCG and no severe immunocompromising condition - consider repeat IGRA if near cutoff point, e.g. TB Ag-Nil < 0.7
  - U.S. born with no risk factors for exposure or progression - repeat IGRA
- If discordant TST/IGRA and severe immunocompromising condition, offer LTBI
- If severe immunocompromising condition and if TST-/IGRA- and abnormal CXR confirmed old TB, offer LTBI treatment
Summary on IGRAs

- Improved specificity over TST
- Appear 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 with positive test for LTBI
  - 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>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>Max: 300 mg</td>
<td>Daily</td>
<td>9 months Preferred for everyone Complete 270 doses within 12 months</td>
</tr>
<tr>
<td></td>
<td>Children/adolescents 10-15mg/kg</td>
<td></td>
<td>6 months “acceptable” for: Immunocompetent adults without scarring on CXR 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>

### LTBI regimens: SF 2013-2014

Cohort: All TB clinic patients starting LTBI treatment from 2013-2014 to present with known treatment end reason.

<table>
<thead>
<tr>
<th></th>
<th>3HP</th>
<th>%</th>
<th>INH</th>
<th>%</th>
<th>INH + RIF</th>
<th>%</th>
<th>RIF</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started Treatment</td>
<td>82</td>
<td>181</td>
<td>34</td>
<td>223</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>62</td>
<td>76%</td>
<td>116</td>
<td>72%</td>
<td>29</td>
<td>85%</td>
<td>161</td>
<td>72%</td>
</tr>
<tr>
<td>Adverse Reaction Chose to Stop/Lost/ Refused</td>
<td>3</td>
<td>4%</td>
<td>2</td>
<td>1%</td>
<td>0</td>
<td>0%</td>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td>Moved</td>
<td>16</td>
<td>20%</td>
<td>42</td>
<td>23%</td>
<td>4</td>
<td>12%</td>
<td>16</td>
<td>16%</td>
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<tr>
<td>Provider Decision</td>
<td>0</td>
<td>0%</td>
<td>3</td>
<td>2%</td>
<td>0</td>
<td>0%</td>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1%</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0%</td>
<td>7</td>
<td>4%</td>
<td>1</td>
<td>3%</td>
<td>19</td>
<td>9%</td>
</tr>
</tbody>
</table>
Drug drug interactions with rifamycins

- ARVs (antiretroviral agents)
- Oral contraception
- Narcotics
- Antipsychotics
- Chemotherapeutic agents
- Immune suppression for organ transplant

The NEW ENGLAND JOURNAL of MEDICINE

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

TBTC Study 26 PREVENT
TB– Design

- Phase 3 trial; n = 8000
- Non-inferiority design
- TST-positive: close contacts, new convertors, HIV-positive, Class 4
- Randomized to:
  - RPT (15 mg/kg) + INH (15 mg/kg) weekly x 12 weeks DOT (3 months) vs.
  - INH 300 mg daily x 9 months
- Children 2 years and older included
LTBI Treatment – the new standard?

- INH/RPT 12 doses compared to INH 9 months
  - 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
Acknowledgements

- Laurel Bristow, SF TB program epidemiologist
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- Payam Nahid, MD, TB Trials Consortium
- San Francisco TB Prevention and Control Program Staff

The real heroes!