Screening for Tuberculosis Infection: Making the Most of Imperfect Tests

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Disclosure

• No disclosures or conflicts of interest
Objectives

• Review features of the main tests for the diagnosis of latent TB infection and TB disease

• List pro’s and con’s of each test

• Describe when to report suspected TB cases to public health
TB Diagnosis – Ideal State

Tests would be
• Sensitive
• Specific
• Rapid
TB Diagnosis – Reality

• Screening tests lack sensitivity
• TB is less common—clinicians need to think TB
• Culture takes weeks
Mycobacterial Burden

Number of Organisms (log scale)

- Incubating
- Latent
- Old, Inactive
- Active
# Latent Infection vs. TB Disease

<table>
<thead>
<tr>
<th>Latent TB Infection (LTBI)</th>
<th>TB Disease (in the lungs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inactive</strong>, tubercle bacilli contained</td>
<td><strong>Active</strong>, tubercle bacilli multiplying</td>
</tr>
<tr>
<td>TST or blood test results usually positive</td>
<td>TST or blood test results usually positive</td>
</tr>
<tr>
<td>Chest x-ray usually <strong>normal</strong></td>
<td>Chest x-ray usually <strong>abnormal</strong></td>
</tr>
<tr>
<td>Sputum smears and cultures <strong>negative</strong></td>
<td>Sputum smears and cultures may be <strong>positive</strong></td>
</tr>
<tr>
<td><strong>No symptoms</strong></td>
<td><strong>Symptoms</strong> such as cough, fever, weight loss</td>
</tr>
<tr>
<td><strong>Not infectious</strong></td>
<td><strong>Often infectious</strong> before treatment</td>
</tr>
<tr>
<td><strong>Not a case</strong> of TB</td>
<td><strong>A case</strong> of TB</td>
</tr>
</tbody>
</table>
**Tuberculin Skin Test (TST)**

- **Requires proper placement**
  - Inject 0.1ml of PPD intradermally in forearm

- **Requires proper reading**
  - Read 48-72hrs post-placement
  - Read induration, not erythema
  - Read diameter across forearm
  - Record results in millimeters
Interferon Gamma Release Assays (IGRAs)

- Blood tests that indirectly detect *M. tb* complex infection
- Expose T cells to 2 or 3 TB antigens. If the T cells were previously sensitized to these antigens they will release interferon-gamma
- These antigens are absent from most non-TB mycobacteria
  - Exceptions: *M. kansasii, M. marinum, M. szulgai*
- Two FDA approved IGRAs commercially available in U.S.
  - QuantiFERON-TB Gold In-Tube
  - T-SPOT.TB
- **PRO’s**: not affected by BCG vaccination, requires one visit
- **CON’s**: increased cost compared to TST, reproducibility?
QuantiFERON-Gold In-Tube (QFT)

Collection and processing considerations

• Draw blood into 3 proprietary 1 ml tubes
• Do not overfill; shake 10 times
• Get tubes at 37°C as soon as possible and w/in 16hrs
• Incubate upright for 16-24hrs
• Centrifuge and carefully remove ≥150 µl plasma to assay
QuantiFERON-Gold In-Tube (QFT)

- **Nil tube**: no additives, used to determine if the patient has a background immune response that could result in a false +. In order for a test to be valid, the nil tube must have a value ≤8.0 IU/ml.

- **Mitogen tube**: contains a non-specific stimulator of T cells, serves as the positive control. In order for test to be valid, the mitogen tube must have a value ≥0.5 IU/ml higher than the value of the nil.

- **TB antigen tube**: assay tube. For a test to be considered positive, the antigen tube value minus the value of the nil tube must be ≥0.35 IU/ml.
QuantiFERON-Gold In-Tube (QFT)

• Test cut-off designed to maximize sensitivity in comparison to culture-positive patients and specificity to people unlikely to have disease

• But no gold-standard for LTBI

• Among individuals with values just above or just below the cut-off threshold, conversions and reversions were common

• Confirming a positive QFT in a low-risk individual may be prudent before starting LTBI therapy

• “Indeterminate” result not equal to “intermediate”
Chest Imaging

- Primary TB infection: infiltrates, hard to distinguish from CAP
- Reactivation TB: apical cavity (left) is classic finding
- Miliary pattern (right) indicates hematogenous spread
Mycobacteriologic Examination

• Proper specimen collection
  • Collect at least 3 sputum specimens at 8-24 hr intervals, at least one should be collected early morning
  • Coughing, induction, bronchoscopy, gastric aspirates
  • Follow infection control precautions during collection

• Acid-fast bacilli (AFB) smear
• Direct identification by nucleic amplification test
• Specimen culturing and identification
• Drug susceptibility
• Genotyping
Acid-Fast Bacilli (AFB) Smear

- Microscopic exam
- Need at least 10,000 AFB/ml to be positive
- Results in 24 hrs
- Positive result supports diagnosis of TB disease; however does not distinguish between viable and dead organisms
- Does not distinguish between MTB and non-tuberculosis mycobacteria
Nucleic Acid Amplification Test (NAAT)

- Performed directly on pulmonary specimen: sputum, bronch, tracheal

- Should be done on a respiratory specimen from each patient with signs and symptoms of active pulmonary TB for whom a diagnosis of TB is being considered

**PRO’s:** earlier diagnosis leads to earlier treatment and reduced period of infectiousness, earlier infection control decisions, earlier public health interventions

**CON’s:** does not replace AFB culture, adds lab cost, is labor intensive, susceptible to contamination
AFB Culture and Identification

- More sensitive than smear: need only 10 AFB/ml for a positive result
- Results as soon as 4-14 days if liquid media used
- Incubate at least 6 wks to confirm no growth
- Once there is growth many labs can do DNA probe identification (*not* amplified)
- Also, biochemical identification
Xpert MTB/RIF Assay

• Is a nucleic acid amplification (NAA) test that uses a disposable cartridge with the GeneXpert Instrument System
• Detects *M. tuberculosis* complex and rifampin resistance
• Sputum from a suspect TB patient is mixed with a reagent and a cartridge containing this mixture is inserted in the machine

• **PRO’s**: Results available in a few *hours*, minimal technical training needed
• **CON**: cost
Case #1

- 61 yr old woman, born in Philippines, in U.S. since 1995
- Cough x 1-2 weeks, dyspnea, 5 lb wt loss, fatigue
- CXR/chest CT: cavitary lesions
- Sputum AFB smear 4+, AFB culture pending

What test will help you most at this juncture?
- TST
- IGRA
- NAA test on sputum
- Bronchoscopy with AFB smear and culture
Case #1 – cont.

- The NAA test is performed directly on the sputum sample and detects *M. tuberculosis* complex RNA
  - Positive result → highly suspicious for TB disease (although still not confirmatory)
  - Negative result → doesn’t rule out TB disease

- TST and IGRA won’t help advance the diagnostic process
- Bronchoscopy only if for some other pulmonary indication

- This patient was NAA+ and was started on 4-drug TB therapy*

* Report case to public health
Case #2

- 69 yr old woman, HIV-, born in Mexico, in U.S. since 1979
- Mild cough and dyspnea x 1 week
- CXR: patchy infiltrates, perihilar lymphadenopathy
- Rx with levofloxacin for CAP
- One month later develops neck mass
- TST = 32mm, QFT = positive (test placed/collected same day)
- 4-drug TB treatment started* upon TST+ and QFT+

- What tests are indicated next?

* Report case to public health
Case #2—cont.

- What tests are indicated next?
  - Chest CT
  - Biopsy of neck mass for AFB smear and culture
  - Ultrasound of neck mass
  - Sputum for AFB smear and culture
  - Urine for AFB smear and culture
Case #2—cont.

- Chest CT
  - Biopsy of neck mass for AFB smear and culture
  - Ultrasound of neck mass
  - Sputum for AFB smear and culture
  - Urine for AFB smear and culture

• Chest CT and neck U/S won’t help advance the diagnostic process
• Urine for AFB smear/culture only if GU symptoms

• This patient was AFB smear negative on lymph node and sputum specimens but grew *M. tuberculosis* from both sites
Case #3

- 49 yr old man, HIV+, born in Mexico, in U.S. since 2004
- Cough, diarrhea w/ melena, weakness, 35lb wt loss over 3 mos.
- Not on HIV meds, CD4 = 2; has diabetes and cirrhosis
- Treated for culture-negative pericardial TB in 2009
Case #3 – cont.

• Duodenal biopsy: AFB seen on the stain but not sent for culture
• CXR – normal
• Chest CT – mild abnl but no cavity, no miliary
• Sputum smear negative
• Therapy for TB and Mycobacterium avium started*

• *Should you order a NAAT on the sputum specimen?*
• *Should you order a TST or IGRA?*

* Report case to public health
Case #3 – cont.

• NAAT would be helpful if positive
• TST or IGRA: positive result would tell you the patient is infected, but negative result doesn’t help b/c of immunocompromised state

• This patient’s sputum grew an AFB which was eventually identified as Mycobacterium avium complex (MAI or MAC)
• TB meds stopped
• No TST, IGRA, or NAAT performed
Case #4

• 25 yr old man, HIV-, born in Guatemala, in U.S. since 2012
• Neck swelling x 1 month; otherwise healthy
• Immigration physical: pt reports TST+, CXR had a “shadow”, no diagnosis of LTBI or TB given

• CXR – nl; chest CT – multiple nodules upper lobes, no cavity
• TST = 40mm
• Lymph node biopsy: necrotic granulomas, AFB smear positive
• 4-drug TB therapy started*

• Should this patient be in airborne isolation?

* Report case to public health
Case #4 – cont.

• Should this patient be in airborne isolation? YES

• How to know when to release from AII room?
  - Sputum smear negative x 3
  - Xpert MTB/RIF negative result x 1
  - Consider at least 5 days of effective TB therapy

• This patient had 3 sputa specimens collected—all were AFB smear negative. One specimen grew an AFB, later identified as *M. kansasii*. 
Conclusions

• Diagnosing TB typically requires multiple tests, interpreted in the clinical context
  ➢ Good communication with your labs
  ➢ Try to build in reflex testing algorithms
  ➢ Consult public health for help

• Collect specimens from as many sites as indicated to increase yield

• Even suspect TB cases are reportable to public health
  ➢ If patient starts TB medications, report
CDPH TB Control Program—Key Points of Contact

• To report cases
  ▪ Juan Elias (Senior Comm Dis Investigator): 312-746-6013
  ▪ Nereida Bruno-Otero (Senior Nurse Case Manager): 312-746-6036

• Clinical consultation
  ▪ Dr. Kathy Ritger: 312-746-5992

• General program information
  ▪ Nancy Rivera (Program Director): 312-746-5987
Self-Help for the Epidemiologist

- I AM SIGNIFICANT
- REJECTING THE NULL, EMBRACING THE WHOLE
- CLEANING YOUR INNER DATA
- DECORATING YOUR 2x2 TABLE
- PUMP YOURSELF UP!
- BE 100% CONFIDENT!