The Diagnosis of Active TB

Deborah McMahan, MD
TB Intensive
September 28, 2017
Agenda

- Epidemiology
- Big picture
- Conditions that Should Make You Suspicious
- Which test? Eenie meenie miny mo
- Radiographic Clues
- More Tests
- Putting it All Together
Big picture
The diagnosis of active TB is heavily dependent on your index of suspicion

- Low prevalence in US
- Multiple high risk populations
- At best TB is a difficult disease to treat, any delay in diagnosis compounds the problem
- THINK TB AND TEST LIKE YOU MEAN IT
Epidemiology
<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>116</td>
<td>109</td>
</tr>
<tr>
<td>Deaths</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Rate</td>
<td>1.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

US Rate 3.00

Tuberculosis worldwide

An estimated 2-3 billion people are infected with the bacillus *Mycobacterium tuberculosis*, only 5-15% will develop the disease.

In 2015
- 10.4 million cases
- 1.8 million deaths
- 480,000 *MDR-TB cases

30 high-burden countries

Incidence rates, 2015

Estimates, new cases per 100,000 population:
- 40 - 99
- 100 - 199
- 200 - 299
- 300 - 499
- 500+

Source: WHO global tuberculosis report 2016
Conditions that Should Make You Suspicious
STAGES OF TB

- **Exposure**
  - 95%
  - 5%
  - Primary/Initial infection
  - Local progression
  - Disseminated disease
  - Miliary TB

- Latent/Dormant infection
  - 5%

- Active or reactivated (recrudescence) TB
From TB Infection to TB Disease

- For healthy adults, if you have TB infection your highest risk (5%) of going from TB infection to TB disease is in the first two years after you have been infected.
- After the first two years, for the rest of your life there is a 5% risk of going from TB infection to TB disease.
- 10% total lifetime risk of developing TB disease.
- The risk is higher for some people.
# High Risk Factors

<table>
<thead>
<tr>
<th>Condition</th>
<th>TB Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>10–100</td>
</tr>
<tr>
<td>Close Contacts</td>
<td>15</td>
</tr>
<tr>
<td>Organ-transplantation recipients</td>
<td>20–70</td>
</tr>
<tr>
<td>Chronic renal failure requiring dialysis</td>
<td>6.9–52.5</td>
</tr>
<tr>
<td>TNF-alpha blockers</td>
<td>1.6–25.1</td>
</tr>
<tr>
<td>Silicosis</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Worldwide, biologics account for about one out of eight prescriptions written and U.S. sales of biologics increased by 20 percent to $40.3 billion in the past year.
## Medium Risk Factors

<table>
<thead>
<tr>
<th>Condition</th>
<th>TB Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibronodular disease on chest x-ray</td>
<td>6–19</td>
</tr>
<tr>
<td>Immigrants from high-TB-prevalence countries</td>
<td>2.9–5.3</td>
</tr>
<tr>
<td>Health-care workers</td>
<td>2.55</td>
</tr>
<tr>
<td>Prisoners, homeless persons, illicit drug users</td>
<td></td>
</tr>
</tbody>
</table>

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4777925/table/tbl1/
## Low Risk Factors

<table>
<thead>
<tr>
<th>Condition</th>
<th>TB Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>1.6–7.83</td>
</tr>
<tr>
<td>Smoking</td>
<td>2–3.4</td>
</tr>
<tr>
<td>Use of corticosteroids</td>
<td>2.8–7.7</td>
</tr>
<tr>
<td>Underweight</td>
<td>2–3</td>
</tr>
</tbody>
</table>

* New evidence regarding diabetes

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4777925/table/tbl1/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4777925/table/tbl1/)
Risk of Progression to Disease

- **TB Infection No risk factors**: Remains latent, TB Disease (10% lifetime risk)
- **TB Infection And Diabetes**: Remains latent, TB Disease (30% lifetime risk)
- **TB Infection And HIV**: Remains latent
- **TB Disease**: (7 – 10% per year)
Risk of developing disease

TB incidence is higher for people with diabetes and much higher and the leading cause of death among people with HIV.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk of Developing TB</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB infection and no risk factors</td>
<td>About 10% over a lifetime</td>
<td>For people with TB infection, no risk factors, and no treatment, the risk is about 5% in the first 2 years after infection and about 10% over a lifetime.</td>
</tr>
<tr>
<td>TB infection and diabetes</td>
<td>About 30% over a lifetime</td>
<td>For people with TB infection and diabetes, and with no treatment, the risk is three times as high, or about 30% over a lifetime.</td>
</tr>
<tr>
<td>TB infection and HIV infection</td>
<td>About 7% to 10% PER YEAR</td>
<td>For people with TB infection and untreated HIV infection and with no LTBI treatment, the risk is about 7% to 10% PER YEAR, a very high risk over a lifetime.</td>
</tr>
</tbody>
</table>

TB and Diabetes

- Diabetes triples a person’s risk of developing tuberculosis.
- The likelihood that a person with TB will die, or that they will get TB again after they have been successfully treated for it, is also significantly higher among people with diabetes.
- Research also shows that among people who are being treated for TB, those with diabetes remain contagious longer than those who do not have diabetes.
TB Risk Factors; Texas

- Foreign Born: 57.9%
- Diabetes: 18.1%
- Alcohol Abuse: 16.6%
- Prison/Jail: 11.2%
- Homeless: 6.7%
- HIV/AIDS: 5.1%
- Health Care Worker: 2.7%
Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

Obesity (BMI ≥30 kg/m²)

1994

2000

2014

Diabetes

1994

2000

2014

CDC’s Division of Diabetes Translation. United States Surveillance System available at http://www.cdc.gov/diabetes/data
TB in US vs Foreign Born
New Tuberculosis (TB) Cases, 22 High-Burden Countries (HBCs), 2012

India: 2,200,000
China: 1,000,000
South Africa: 530,000
Indonesia: 460,000
Pakistan: 410,000
Bangladesh: 350,000
Philippines: 260,000
Ethiopia: 230,000
Congo (Dem. Republic of): 210,000
Myanmar: 200,000
Nigeria: 180,000
Mozambique: 140,000
Viet Nam: 130,000
Russian Federation: 130,000
Kenya: 120,000
Brazil: 92,000
Thailand: 80,000
Tanzania (United Rep. of): 79,000
Zimbabwe: 77,000
Uganda: 65,000
Cambodia: 61,000
Afghanistan: 56,000

Total New TB Cases in the 22 High-Burden Countries = 7,000,000

Figure 2. TB Rates by Race/Ethnicity, 2014

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Rate per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>17.9</td>
</tr>
<tr>
<td>Black</td>
<td>5.1</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5.0</td>
</tr>
<tr>
<td>White</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Percentage of TB Cases Among Foreign-born Persons, United States*

2004

2014

*Updated as of June 5, 2015.
Moral of the Story

- Expanding risk factors to take into consideration when evaluating a patient with pneumonia, pleural effusion or lymphadenopathy

- THINK TB
Diagnosis of Active

Step One

Take a Great History
Which test? Eenie meenie miny mo
New TB Testing Recommendations

- American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America searched, selected, and synthesized relevant evidence to draft recommendations that were then graded by the group.


TB Skin Test

- Sensitivity is high (95%–98%).
- False-negative reactions occur more frequently in:
  - Infants and young children
  - Early (<6–8 weeks) after infection
  - Persons having recently received viral vaccination
  - Persons with clinical conditions associated with immunosuppression or overwhelming illness (including TB)
  - Persons with recent viral and bacterial infections
  - Association with treatment with immunosuppressive drugs (eg, high-dose corticosteroids, TNF inhibitors).

Injection of PPD

(a)

Epidermis

Dermis

Small bleb develops

5–9 mm
Positive if person is in category 1

10–14 mm
Positive if person is in category 2

≥15 mm
Positive if person is in category 3

(b)
Baseline skin test

- What is the Reaction?
  - Negative: Retest 1-3 weeks later
    - Negative: Person probably does NOT have TB infection
      - Repeat TST at regular intervals; a positive reaction could be due to a recent TB infection.
    - Positive: What is the Reaction?
  - Positive: Person probably has TB infection
    - Follow-up for positive TST and evaluate for LTBI treatment
  - Positive: The reaction is considered a boosted reaction (due to TB infection that occurred a long time ago). Note: The person does have LTBI; a decision must be made whether to treat or not.

- Positive: Follow-up for positive TST and evaluate for LTBI treatment
Diagnosis of TB - IGRAs

- IGRAs use a single specimen of peripheral blood that is drawn and incubated overnight with specific antigens for M. tuberculosis; interferon-γ production is then determined.
- The QFT test measures the amount of interferon-γ in the supernatant of a cell suspension, whereas the T-SPOT test determines the number of cells producing interferon-γ with the use of an ELISpot assay.

https://static1.squarespace.com/static/52c5f4ade4b02052b13a2eac/t/53253ac1e4b08fd5fbc4479b/1394948801465/LTBI-rv+nejm+2011.pdf
Diagnosis of TB - IGRAs

- IGRAs appear to be somewhat more specific and less sensitive for predicting future disease than the tuberculin skin test, but the differences are modest.
- Both types of test have low positive and high negative predictive values.
- Because both IGRAs and the TST rely on an intact immune response, both are likely to have reduced sensitivity when used in persons with immunosuppression.

https://static1.squarespace.com/static/52c5f4ade4b02052b13a2eac/t/53253ac1e4b08fd5fbc4479b/1394948801465/LTBI+rv+nejm+2011.pdf
Diagnosis of TB - IGRAs

- Whereas the tuberculin skin test may be more likely to identify persons with longstanding cellular immune responses to TB antigens, IGRAs are more likely to be positive in persons who have recently been infected with M. tuberculosis, which is a group at particularly high risk for progression to disease.

- Also no cross reactivity with BCG

https://static1.squarespace.com/static/52c5f4ade4b02052b13a2eac/t/53253ac1e4b08fd5fbc4479b/1394948801465/LTBI+rv+nejm+2011.pdf
IGRA

- A recent study found that a change of QuantiFERON-TB interferon (IFN)γ values from <0.2 to >0.7 IU/mL is associated with an increased incidence in the rate of tuberculosis.
- The incidence rates of tuberculosis were 10-fold higher for individuals who had a change in QuantiFERON-TB IFNγ values from <0.2 to >0.7 IU/mL, compared to those who maintained values <0.2 IU/mL over 2 years ($P = .0003$).

Overall, 87% of patients with active TB had IFNγ values >0.7 IU/mL.

http://www.infectiousdiseaseadvisor.com/respiratory/tuberculosis-detection-may-improve-with-conversion-value-change/article/679807/?DCMP=EMC-IDA_Update_20170905&cpn=id_md%2cid_all&hmSubId=&hmEmail=Wmi4BbkAIgtn4ikxvTRfU4IMMI-xHN400&NID=1487610358&dl=0&spMailingID=18002136&spUserID=MTgwMTYxMDg3OTQ5S0&spJobID=1100054603&spReportId=MTEwMDA1NDYwMwS2
TST or IGRA?

- Populations in which IGRAs are preferred for testing:
  - Persons who have received BCG (either as a vaccine or for cancer therapy); and
  - Persons from groups that historically have poor rates of return for TST reading.
- TST is preferred over IGRAs for testing children less than 5 years of age.

https://www.cdc.gov/tb/publications/factsheets/testing/igra.htm
Strong Recommendation

They recommend performing an **IGRA** rather than a TST in individuals 5 years or older who meet the following criteria:

1. are likely to be infected with *Mtb*
2. have a low or intermediate risk of disease progression
3. it has been decided that testing for LTBI is warranted
4. either have a history of BCG vaccination or are unlikely to return to have their TST read

Remarks: A TST is an acceptable alternative, especially in situations where an IGRA is not available, too costly, or too burdensome.

Conditional Recommendation

They suggest performing an IGRA rather than a TST in all other individuals 5 years or older who are:

1) likely to be infected with *Mtb*
2) who have a low or intermediate risk of disease progression
3) and in whom it has been decided that testing for LTBI is warranted

Remarks: A TST is an acceptable alternative, especially in situations where an IGRA is not available, too costly, or too burdensome.
Diagnosis of Active

Step One
Take a Great History

Step Two
Obtain TST or IGRA
Radiographic Clues
Primary Pulmonary TB

- Parenchymal disease
  - usually manifests as dense, homogeneous parenchymal consolidation **in any lobe**
  - however, predominance in the lower and middle lobes (subpleural sites) is suggestive of the disease, especially in adults
- Lymphadenopathy
- Miliary opacities
- clustered parenchymal opacification may give a galaxy sign
- Pleural effusion (30-40% of cases in Adults; 15% Peds)

https://radiopaedia.org/articles/tuberculosis-pulmonary-manifestations-1
Primary TB

Miliary TB

https://radiopaedia.org/articles/tuberculosis-pulmonary-manifestations-1
Primary Pulmonary TB

- In approximately two-thirds of cases, the parenchymal focus resolves without sequelae.
- In the remaining cases, a radiologic scar persists that can calcify in up to 15% of cases, an entity that is known as a Ghon focus.
- Other calcified foci can also be seen, and persistent mass like opacities called tuberculomas are seen in ~10% of cases.

https://radiopaedia.org/articles/tuberculosis-pulmonary-manifestations-1
Reactivation (Post Primary)
Pulmonary TB

In the majority of cases, post-primary TB within the lungs develops in either:

- Posterior segments of the upper lobes
- Superior segments of the lower lobes
- Typical appearance of post-primary TB is that of patchy consolidation or poorly defined linear and nodular opacities

- Hilar Lymph nodes in 30% of cases

https://radiopaedia.org/articles/tuberculosis-pulmonary-manifestations-1
Reactivation (Post Primary) Pulmonary TB

- Reactivation TB is far more likely to cavitate than primary infections and are seen in 20-45% of cases.
- In the vast majority of cases, they develop in the posterior segments of the upper lobes (85%)
- Endobronchial spread along nearby airways is a relatively common finding, resulting in a relatively well-defined 2-4 mm nodules or branching lesions (tree-in-bud sign) on CT

https://radiopaedia.org/articles/tuberculosis-pulmonary-manifestations-1
Cavitary TB
Diagnosis of Active

- **Step One**: Take a Great History
- **Step Two**: Obtain and IGRA or TST
- **Step Three**: Obtain a Chest X-ray
More Tests
Strong Recommendation

We recommend that acid-fast bacilli (AFB) smear microscopy be performed, rather than no AFB smear microscopy, in all patients suspected of having pulmonary TB. Providers should request a sputum volume of at least 3 mL, but the optimal volume is 5–10 mL. Concentrated respiratory specimens and fluorescence microscopy are preferred.

- Negative results do not exclude pulmonary TB.
- Similarly, false-positive results are sufficiently common that a positive AFB smear result does not confirm pulmonary TB.

Sputum

- Three sputum for AFB smear and culture and PCR q am time three
- If rushed, q 8 hours times three

Please do not order one smear!

Please do not order a culture only!
Conditional Recommendation

They suggest that both liquid and solid mycobacterial cultures be performed, rather than either culture method alone, for every specimen obtained from an individual with suspected TB disease (conditional recommendation, low-quality evidence).

Remarks: The conditional qualifier applies to performance of both liquid and solid culture methods on all specimens. At least liquid culture should be done on all specimens as culture is the gold standard microbiologic test for the diagnosis of TB disease. The isolate recovered should be identified according to the Clinical and Laboratory Standards Institute guidelines and the American Society for Microbiology Manual of Clinical Microbiology.

Conditional Recommendation

They suggest performing a diagnostic nucleic acid amplification test (NAAT), rather than not performing a NAAT, on the initial respiratory specimen from patients suspected of having pulmonary TB.

PLEASE PLEASE PLEASE PLEASE order a PCR (NAAT) on all sputum
What is a NAAT?

- Nucleic acid amplification test (NAAT) is a testing method that detects the genetic material (nucleic acid) of the bacteria causing the infection.

- It does this in part by amplifying or making numerous copies of the genetic material so that the detection system can identify the presence of the bacteria.
Strong Recommendation

They recommend performing rapid molecular drug susceptibility testing for rifampin with or without isoniazid using the respiratory specimens of persons who are either AFB smear positive or Hologic Amplified MTD positive and who meet one of the following criteria:

1. have been treated for tuberculosis in the past,
2. were born in or have lived for at least 1 year in a foreign country with at least a moderate tuberculosis incidence (≥20 per 100,000) or a high primary multidrug-resistant tuberculosis prevalence (≥2%)
3. are contacts of patients with multidrug-resistant tuberculosis, or
4. are HIV infected.

Remarks: This recommendation specifically addresses patients who are Hologic Amplified MTD positive because the Hologic Amplified MTD NAAT only detects TB and not drug resistance; it is not applicable to patients who are positive for types of NAAT that detect drug resistance, including many line probe assays and Cepheid Xpert MTB/RIF.

Molecular Drug Susceptibility

- The test simultaneously detects Mycobacterium tuberculosis complex (MTBC) and resistance to rifampin (RIF) in less than 2 hours.
- In comparison, standard cultures can take 2 to 6 weeks for MTBC to grow and conventional drug resistance tests can add 3 more weeks.
- Quicker results provide timely that aids in selecting treatment regimens and reaching infection control decisions quickly.

Conditional Recommendation

They suggest mycobacterial culture of respiratory specimens for all children suspected of having pulmonary TB.

Remarks: In a low incidence setting like the United States, it is unlikely that a child identified during a recent contract investigation of a close adult/adolescent contact with contagious TB was, in fact, infected by a different individual with a strain with a different susceptibility pattern. Therefore, under some circumstances, microbiological confirmation may not be necessary for children with uncomplicated pulmonary TB identified through a recent contact investigation if the source case has drug-susceptible TB.
Smear
Culture
PCR
Conditional Recommendation

They suggest sputum induction rather than flexible bronchoscopic sampling as the initial respiratory sampling method for adults with suspected pulmonary TB who are either unable to expectorate sputum or whose expectorated sputum is AFB smear microscopy negative.

Conditional Recommendation

They suggest flexible bronchoscopic sampling, rather than no bronchoscopic sampling, in adults with suspected pulmonary TB from whom a respiratory sample cannot be obtained via induced sputum.

Remarks: In the committee members’ clinical practices, bronchoalveolar lavage (BAL) plus brushings alone are performed for most patients; however, for patients in whom a rapid diagnosis is essential, transbronchial biopsy is also performed.
Smear  Culture  PCR
Conditional Recommendation

They suggest that postbronchoscopy sputum specimens be collected from all adults with suspected pulmonary TB who undergo bronchoscopy.

Remarks: Postbronchoscopy sputum specimens are used to perform AFB smear microscopy and mycobacterial cultures.
Conditional Recommendation

They suggest flexible bronchoscopic sampling, rather than no bronchoscopic sampling, in adults with suspected miliary TB and no alternative lesions that are accessible for sampling whose induced sputum is AFB smear microscopy negative or from whom a respiratory sample cannot be obtained via induced sputum.

Conditional Recommendation

Remarks: Bronchoscopic sampling in patients with suspected miliary TB should include bronchial brushings and/or transbronchial biopsy, as the yield from washings is substantially less and the yield from BAL unknown.

For patients in whom it is important to provide a rapid presumptive diagnosis of tuberculosis (ie, those who are too sick to wait for culture results), transbronchial biopsies are both necessary and appropriate.

Smear  Culture  PCR
Guidelines for Testing for Extrapulmonary TB
Conditional Recommendation

They suggest that cell counts and chemistries be performed on amenable fluid specimens collected from sites of suspected extrapulmonary TB.

Remarks: Specimens that are amenable to cell counts and chemistries include pleural, cerebrospinal, ascitic, and joint fluids.
Conditional Recommendation

They suggest that adenosine deaminase (ADA) levels be measured, rather than not measured, on fluid collected from patients with suspected pleural TB, TB meningitis, peritoneal TB, or pericardial TB.

Also suggest that free IFN-γ levels be measured, rather than not measured, on fluid collected from patients with suspected pleural TB or peritoneal TB.
What is ADA?

- Adenosine deaminase (ADA) is a protein that is produced by cells throughout the body and is associated with the activation of lymphocytes, a type of white blood cell that plays a role in the immune response to infections.
- Activity of this enzyme increases in TB patients.
How is ADA Collected?

- A sample of pleural fluid is collected by a healthcare practitioner with a syringe and needle using a procedure called thoracentesis.
- Rarely, other body fluid samples, such as peritoneal or cerebrospinal fluid (CSF), are collected using procedures specific to the fluid type.

What is Interferon Gamma?

- Interferon gamma (IFN-γ), a cytokine produced by a variety of cells is involved in the immune response against M. tuberculosis.
- It activates the production of other cytokines and molecules that kill mycobacterium.

Conditional Recommendation

They suggest that AFB **smear microscopy** be performed, rather than not performed, on specimens collected from sites of suspected extrapulmonary TB.

**Remarks:** A positive result can be used as evidence of extrapulmonary TB and guide decision making because false-positive results are unlikely. However, a negative result may not be used to exclude TB because false-negative results are exceedingly common.
Conditional Recommendation

They recommend that mycobacterial cultures be performed, rather than not performed, on specimens collected from sites of suspected extrapulmonary TB.

**Remarks:** A positive result can be used as evidence of extrapulmonary TB and guide decision making because false-positive results are unlikely. However, a negative result may not be used to exclude TB because false-negative results are exceedingly common.

Conditional Recommendation

They suggest that **NAAT be performed**, rather than not performed, on specimens collected from sites of suspected extrapulmonary TB.

**Remarks**: A positive NAAT result can be used as evidence of extrapulmonary TB and guide decision making because false-positive results are unlikely. However, a negative NAAT result may not be used to exclude TB because false-negative results are exceedingly common. At present, NAAT testing on specimens other than sputum is an off-label use of the test.

Conditional Recommendation

They suggest that histological examination be performed, rather than not performed, on specimens collected from sites of suspected extrapulmonary TB.

Remarks: Both positive and negative results should be interpreted in the context of the clinical scenario because neither false-positive nor false-negative results are
Strong Recommendation

They recommend one culture isolate from each mycobacterial culture-positive patient be submitted to a regional genotyping laboratory for genotyping.

Benefits of Genotyping

- Genotyping is useful in detecting false-positive results due to confirming laboratory cross-contamination
- Investigating outbreaks of TB (both detecting unsuspected outbreaks and confirming suspected outbreaks)
- Evaluating contact investigations.
- Determining whether new episodes of TB are due to reinfection or reactivation.

Diagnosis of Active

Step One: Take a Great History

Step Two: Obtain and IGRA or TST

Step Three: Obtain a Chest X-ray

Order the right tests

Step Four
Putting it All Together
Putting it All Together

- Starts with you being a great clinician -- THINK TB
- TST or IGRA
- Radiographs
- Samples – sputum, tissue or fluid – get the right tests
- Then the easy part – treat the patient
Summary
Summary

- TB is more common than you think
- Requires a good diagnostician
- Appropriate testing
- Observed treatment
Diagnosis of Active

Step One
Take a Great History

Step Two
Obtain and IGRA or TST

Step Three
Obtain a Chest X-ray

Order the right tests

Step Four

Step Five