Clinical Presentation and Diagnosis of Tuberculosis

Virtual TB intensive
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Conflict of Interest Disclosure Statement

- Neither I, nor my spouse/partner have/had financial or other relationships with ANY commercial interest organizations within the past 12 months.
Overview

- Clinical presentation of active TB
- Principles of establishing TB diagnosis
- Approaches to patients who are suspected of having active TB
Clinical Presentation of TB
Sites of TB:
Pulmonary vs. Extrapulmonary

In the US (CDC)

- Pulmonary: 70%
- Extrapulmonary: 20%
- Both: 10%
“Classic” Clinical Presentation of TB

- **Insidious onset, chronic course**
- **Chest symptoms**
  - Cough (usually productive)
  - Hemoptysis
  - Chest pain (usually pleuritic)
- **Constitutional symptoms**
- **Extrapulmonary symptoms**
Time course after exposure:
Primary vs. post-primary

- **Primary TB:**
  Results from an initial infection with *M. tuberculosis* (recent infection)

- **Post-primary TB** (also called reactivation TB):
  Results from reactivation of latent infection (remote infection)
Right hilar adenopathy in a child whose mother was diagnosed with pulmonary TB
Post-primary:
Pulmonary TB with cavitation
But, TB presentation may not be straightforward
HIV infected TB patient:
sputum AFB smear negative, but high TB bacillary burden
Radiographs of Typical and Atypical Pulmonary TB

Geng, E. et al. JAMA 2005;293:2740
## Radiographic Patterns: Pulmonary TB

<table>
<thead>
<tr>
<th>Finding</th>
<th>“Typical” ( Reactivation )</th>
<th>“Atypical” (child, HIV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opacity</td>
<td>85% Upper</td>
<td>60% Upper</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40% Lower</td>
</tr>
<tr>
<td>Cavitation</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>Uncommon</td>
<td>Common (Unilateral &gt; Bilateral)</td>
</tr>
<tr>
<td>Effusion</td>
<td>May be present</td>
<td>May be present</td>
</tr>
</tbody>
</table>
Class B1 immigrant:
Asymptomatic. Sputum AFB smear negative x 3. Unchanged compared to the CXR 5 month ago

Does he have active TB?

A. Yes
B. No
C. I can’t tell
Natural History of pulmonary TB: “Chronic spreaders”

- Death, 60%
- Chronic, 20%
- Cure, 30% *Not stable cure

*Not stable cure
Clinical presentation of active TB is influenced by the degree of immunosuppression.
Spectrum of TB

Latent TB infection

Pauci-bacillary disease

Disseminated disease in HIV

Asymptomatic “Class B1” immigrants

Cavitary, high-burden disease
Diagnosis of active TB: Fundamental principle

- Rapid and accurate diagnosis of TB is essential for the patient and also to protect the public, especially in patients with pulmonary TB.
Three steps:

1. Risk of exposure/infection
2. Risk of progression to TB
   - Exposure
   - TB infection
   - Active TB disease
Diagnostic process
The first step: suspicion

◆ Exposure risk:
  • Those from high TB incidence countries
  • Homelessness, correctional facilities, institutional residence, substance abuse (→ check local epidemiology)

◆ Progression risk:
  • HIV and other immunosuppression (e.g., TNF-alpha inhibitors)
  • Recent TB infection
  • CXR suggestive of prior untreated TB (apical fibrosis)

“Membership in a risk group”
### The Second Step: Symptoms of Pulmonary TB

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>Cough (dry/productive sputum)</td>
<td>75-80%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>45-75%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>60-70%</td>
</tr>
<tr>
<td>Fever</td>
<td>50-60%</td>
</tr>
<tr>
<td>Night sweats</td>
<td>50-55%</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>25-35%</td>
</tr>
<tr>
<td>No symptoms</td>
<td>10-20%</td>
</tr>
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</table>

Barnes 1988, Miller 2000
Clinical Presentation of TB

Remember: wide range of TB presentation

- TB can involve any organ.
- Severity of symptoms: none to overwhelming
- Tempo of disease progression: ranges from indolent to rapid
- Symptoms and findings: local and/or systemic
- Presentation is often atypical in the immunocompromised (e.g., HIV, even diabetes).
Diagnostic process - Summary

- Epidemiologic or medical risk factors
  “Membership in a risk group”
- Clinical presentation
  - symptoms suggestive of TB?
  - Imaging suggestive of TB?
- Yes? → Obtain appropriate specimens for AFB smear & culture, plus NAAT/PCR
  (Lab confirmation)

Note: no TST or IGRA
TST or IGRA results do not make or break the diagnosis of active TB (sensitivity: ~80%).
PCP calls you and would like to refer a patient to your TB clinic because he may have TB

- History: 55 yo man
  - Born in the Philippines and came to the US 10 years ago ("membership": epi or medical risk)
  - Has had a cough for a month, lost appetite (Symptoms)
Clinical Infectious Diseases

Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children


1Oregon Health & Science University, Portland, Oregon, 2Emory University School of Medicine and Centers for Disease Control and Prevention, Atlanta, Georgia, 3Denver Public Health Department, Denver, Colorado, 4National Jewish Health and the University of Colorado Denver, 5California Department of Public Health, Richmond; 6St James’s Hospital, Dublin, Ireland; 7Francis J. Curry International TB Center, San Francisco, California; 8Foundation for Innovative New Diagnostics, Geneva, Switzerland; 9McGill University and McGill International TB Centre, Montreal, Canada; 10University of Southampton, United Kingdom; 11National Jewish Health, Denver, Colorado; 12Vanderbilt University School of Medicine, Vanderbilt Institute for Global Health, Nashville, Tennessee; 13Wisconsin State Laboratory of Hygiene, Madison, and 14University of Arkansas for Medical Sciences, Little Rock

Published in 2017
Sputum collection

- Spontaneous sputum expectoration
  - 3 specimens (morning preferred)
- If unable to expectorate sputum, use sputum induction using hypertonic saline.
- Consider sputum induction if expectorated sputum is AFB smear negative and NAAT negative.
Obtain bronchoscopic sampling in patients with suspected pulmonary TB when a specimen cannot be obtained even with sputum induction.

Post-bronchoscopy sputum specimens should be collected from all patients with suspected pulmonary TB who undergo bronchoscopy.
# Laboratory diagnosis: Pulmonary TB

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<th>Sensitivity</th>
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<tr>
<td>AFB smear</td>
<td>50-60%</td>
</tr>
<tr>
<td>AFB culture</td>
<td>90-95%</td>
</tr>
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</table>
| Nucleic Acid Amplification Test (NAAT) or PCR| Smear positive: 95%
|                                             | Smear negative: 65% |
Laboratory Diagnosis: Culture

- Guidelines: Both liquid and solid cultures should be performed.
  - MGIT vs. Solid → higher sensitivity (88% vs. 76%) and shorter time to detection (13 vs. 26 days)
  - Solid Media → safeguard for contamination
  - Reporting of the final results: up to 8 – 10 weeks

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<th>Culture media</th>
<th>Time to detection</th>
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<td><strong>Solid:</strong></td>
<td></td>
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<tr>
<td>Egg-based media (e.g. Lowenstein-Jensen)</td>
<td>Average 3 - 4 weeks</td>
</tr>
<tr>
<td>Agar-based media (e.g. Middlebrook 7H10)</td>
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<tr>
<td><strong>Liquid:</strong></td>
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<td>Mycobacterial growth indicator tube (MGIT)</td>
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Nucleic acid amplification tests (NAAT)

- FDA-approved direct amplification tests
  - Amplified MTD and Xpert Mtb/RIF
- Use directly on specimens: the result < 1 day (quick turnaround time)
- Caution: in patients with
  - Current TB treatment > 7 days
    - false-negative in pauci-bacillary TB
  - Prior TB treatment within past 12 months
    - false-positive
NAAT : Guidelines

• NAAT should be performed on the initial respiratory specimen when pulmonary TB is suspected.
  • AFB smear positive pulmonary TB cases
    NAAT - sensitivity 96%, specificity 85%
    (i.e., AFB smear positive, NAAT negative → TB unlikely)
  • AFB smear negative pulmonary TB cases:
    NAAT - sensitivity 66%, specificity 98%
    (i.e., AFB smear negative, but high clinical suspicion, NAAT positive → it’s TB!)
The utility of NAAT depends on the AFB smear results and clinical suspicion (i.e., pre-test probability).

- High suspicion $\rightarrow$ positive NAAT confirms TB.
- Smear positive, low suspicion (NTM suspected) $\rightarrow$ negative NAAT supports NTM diagnosis.
- When AFB smear is negative and clinical suspicion is low, don’t use NAAT because of ↑ false-positive.
The role of TST and IGRA in TB diagnosis

Measures T-cell response to TB antigen

Requires a functional immune system

Positive in ~80% of patients with active TB disease.

TST or IGRA results do not make or break the diagnosis of active TB disease.
CDC definition: “Confirmed TB Case”

- **Laboratory case definition**
  - *M. tuberculosis* by culture or NAAT, or
  - AFB smear + (if culture not obtained)
  
  **OR**

- **Clinical case definition**
  1. Positive TST or IGRA, **AND**
  2. Compatible signs/symptoms/imaging findings, **AND**
  3. Response to treatment with 2 or more TB meds, **AND**
  4. Completed diagnostic evaluation
In the US (CDC)

- Positive Cx: 77%
- Positive smear: 1%
- Positive NAA: 2%
- Provider diagnosis: 5%
- Clinical case definition: 15%
Urgent care calls you about a 40 yo man

- Lives in a homeless shelter
- Cough x one month

Sputum AFB smear positive
NAAT was not ordered

Your plan?
Urgent care call you about a 75 yo woman

- US born. She lives with her husband in a rural area
- Otherwise, no concurrent medical conditions.
- Cough x one month

Sputum AFB smear positive
NAAT was not ordered

Your plan?
Approach to a smear-negative patient when the lab reports AFB growth

- **High**
  - Initiate Rx
  - Isolation

- **Uncertain**
  - Consider Rx if benefits > risks
  - 1. Risk of progression
  - 2. Risk of transmission

- **Low**
  - No Rx
  - Wait for final ID.
  - Probably no isolation

Review epi and progression risk factors as well as imaging → Level of clinical suspicion
Is this TB?

60 yo man with COPD, US-born
• Cough x one month
• Has been in jail
  (estimated 150 jail contacts)
• Treatment for MAC two years ago

AFB smear positive
Your plan?
While you are waiting for confirmation of TB diagnosis…

1. Isolation?
2. Initiation of empiric TB treatment?
3. Evaluation of exposed contacts?
Isolation

- Home isolation in a community
- “TB motel”
- Isolation at a hospital
Initiation of Presumptive TB Treatment

- Consider:
  - Likelihood of TB diagnosis
  - Severity of illness
  - Transmission risk
  - Risk of side effects
Evaluation of exposed contacts

- Generally we can wait until we are certain about the diagnosis
- High-risk contacts (e.g., young children, severely immunocompromised)
- High-profile investigations
Diagnostic Process:
Other consideration

- Pulmonary vs. extrapulmonary
- Community risk
  - Environment where the patient spends a lot of time (e.g., work, home)
Summary: Pulmonary TB

- Wide range of clinical presentation
  - Different levels of public health implication
- Presumptive treatment based on likelihood of TB diagnosis, estimated infectiousness, environment, and severity of illness.
- Communication with TB labs is crucial.
Extrapulmonary TB
U.S. TB Cases by Site of Disease, 2019

- Pulmonary Involvement* 79%
- Extrapulmonary Only 21%

*Any pulmonary involvement which includes cases that are pulmonary only and both pulmonary and extrapulmonary. Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.

Note: Percentages are rounded.
Extrapulmonary TB: In general

Bacillary burden: often low

Imaging: CT/MRI

Diagnostic specimens:
- Fluid analysis: Serous cavity fluids, Joint fluids, CSF
- Abnormal lesion: Fine-needle aspiration, Core needle biopsy, Excisional/surgical biopsy

Sampling: often single; often no follow up

Tests: AFB smear & culture, NAAT, cytology/histopathology,
- Fluid: Cell count and diff, Protein, Glucose, ADA, γ-IFN
Lymph node TB (TB lymphadenitis)

- Classic presentation:
  Isolated chronic painless lymphadenopathy
- Systemic symptoms are uncommon.
- TB lymphadenitis in the cervical region is known as “scrofula”.
TB lymphadenitis: Diagnosis

- AFB smear and culture AND histopathology of lymph node material. Consider NAAT/PCR.
- Fine needle aspiration (FNA) is appropriate for initial evaluation of cervical lymphadenopathy → yield up to 80%
- Consider excisional lymph node biopsy when FNA is not diagnostic, or non-TB diagnosis is likely (e.g., lymphoma)
- Excisional biopsy is preferred over incisional biopsy (sinus tract formation)
Pleural TB

- Early in the course of TB infection, a few organisms may gain access to the pleural space → hypersensitivity response → pleural effusion

- Symptoms:
  - Fever, pleuritic chest pain ("primary TB")
  - If advanced, dyspnea
  - can be asymptomatic

- TST/IGRA: negative in > 20%
Pleural TB: pleural fluid analysis

- Exudate: lymphocyte-predominant
- AFB smears almost always negative
- Culture positive in ~40% of cases
  - NAAT/PCR: close to culture results
- ADA (adenosine deaminase) level:
  - if very low, probably not TB (high sensitivity)
  - If high, can be TB, but low specificity
Sputum exam in pleural TB

- **With infiltrates**, AFB smears (+) in ~50%, and culture positive in ~90%
- **Without infiltrates**, sputum AFB smears are almost always negative, and culture positive in ~20%
CNS TB

1. TB meningitis
2. Intracranial tuberculoma
Summary: Extrapulmonary TB

- Establish TB diagnosis by obtaining specimens
  - Empiric treatment without having AFB specimens should be discouraged.
- Evaluate for pulmonary disease. CXR should be obtained even if you are not suspecting concurrent pulmonary TB. Consider obtaining sputum specimens even with normal CXR.