Clinical Presentation and Diagnosis of Tuberculosis

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No financial conflicts

Overview

- Clinical presentation of active TB
- Principles and process of TB diagnosis
- Approaches to patients who are suspected of having active TB
Clinical Presentation of TB

Sites of TB: Pulmonary vs. Extrapulmonary

- Pulmonary: 70%
- Extrapulmonary: 20%

CDC 2016
Sites of Extrapulmonary TB
US 1993-2006

“Classic” Clinical Presentation of TB

- Insidious onset, chronic course
- Chest symptoms
  - Cough (usually productive)
  - Hemoptyisis
  - Chest pain (usually pleuritic)
- Nonspecific constitutional symptoms
- Extrapulmonary symptoms

Clin Infect Dis 2009;49:1350-7
Time course after exposure: Primary vs. postprimary

- **Primary TB**: results from an initial infection with tubercle bacilli
  - due to recent infection
- **Postprimary TB** (also called *adult-type*, or *reactivation TB*): results from endogenous reactivation of latent infection
  - due to remote infection

Right hilar adenopathy in a child whose mother was diagnosed with pulmonary TB
Post-primary: Pulmonary TB with cavitation

But, presentation of TB may not be straightforward
Natural History of TB: “Chronic spreaders”

*Not stable cure

HIV infected TB patient: sputum smear negative, but high bacillary burden
Radiographs of Typical and Atypical Pulmonary Tuberculosis

Geng, E. et al. JAMA 2005;293:2740-2745

Radiographic Patterns: Pulmonary TB

<table>
<thead>
<tr>
<th>Finding</th>
<th>“Typical” (Reactivation)</th>
<th>“Atypical” (child, HIV)</th>
</tr>
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<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>Children common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Unilateral &gt; Bilateral)</td>
</tr>
<tr>
<td>Effusion</td>
<td>May be present</td>
<td>May be present</td>
</tr>
</tbody>
</table>
Clinical presentation of active TB is influenced by degree of immunosuppression.
Diagnosis of TB: Fundamental principles

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

Three steps

- Exposure
- TB infection
- Active TB disease
Diagnostic process
The first step: suspicion

- Epidemiologic or medical risk factors
  “Membership in a risk group”
  - Foreign-born from high prevalence areas
  - Substance abuse, homelessness, correctional facilities, institutional residence
  - HIV and other immunosuppression (e.g., TNF-alpha inhibitors)
  - CXR suggestive of prior TB (apical fibrosis)

Diagnostic Process
The Second Step: Symptoms of Pulmonary TB

- Cough (dry/productive sputum) 75-80%
- Weight loss 45-75%
- Fatigue 60-70%
- Fever 50-60%
- Night sweats 50-55%
- Hemoptysis 25-35%
- No symptoms 10-20%

Barnes 1988, Miller 2000
Clinical Presentation of TB

Remember: TB can be tricky
- TB can involve any organ or tissue
- Severity of symptoms: none to overwhelming
- Tempo of illness: ranges from indolent to rapid
- Symptoms and findings: local and/or systemic
- Presentation is often atypical in immunocompromised (e.g., HIV, even diabetes)
- TST or IGRA results do not make or break diagnosis of active TB

Diagnostic process

- Epidemiologic or medical risk factors
  - Membership in a risk group, or an individual risk
- Clinical presentation
  - symptoms suggestive of TB?
  - Imaging suggestive of TB?
Clinical Presentation and Diagnosis of Tuberculosis

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 and culture
  (Lab confirmation)
50 yo man is sent to your clinic because he may have TB

- History
  - Has had cough x one month, lost appetite
  - Born in the Philippines and came to the US 10 years ago

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

Published in 1/2017
Collection of respiratory specimens

- Spontaneous sputum expectoration
  - 3 specimens (morning preferred)

- Sputum induction (hypertonic saline) if unable to expectorate sputum or expectorated sputum is AFB smear (and NAAT) negative

Bronchoscopy: Guidelines

- Obtain bronchoscopic sampling, rather than no bronchoscopic sampling, in individuals with suspected pulmonary TB from whom a respiratory sample cannot be obtained via induced sputum.
- Post-bronchoscopy sputum specimens should be collected from all individuals with suspected pulmonary TB who undergo bronchoscopy.
Diagnostic process: Pulmonary TB

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>AFB smear</td>
<td>50-60%</td>
</tr>
<tr>
<td>AFB culture</td>
<td>90-95%</td>
</tr>
<tr>
<td>Nucleic Acid Amplification Test (NAAT)</td>
<td>75-80%</td>
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For culture-positive pulmonary TB cases,
the sensitivity of one smear 55%
  two smears 66%
  three smears 70%

Laboratory Diagnosis: Culture

<table>
<thead>
<tr>
<th>Culture media</th>
<th>Time to detection</th>
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<tbody>
<tr>
<td>Solid: 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>
<td></td>
</tr>
<tr>
<td>Mycobacterial growth indicator tube (MGIT)</td>
<td>Average 10 -14 days</td>
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- 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
  - Final of the combination: up to 6 – 8 weeks
Nucleic acid amplification tests (NAAT)

- FDA-approved direct amplification tests
  - Gen-Probe/MTD and Xpert Mtb/RIF
- Use directly on specimens, result < 1 day
- Caution: in patients with
  - Current TB treatment > 7 days → false-negative
  - 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: sensitivity 96%, specificity 85% (i.e., AFB smear positive, NAAT negative → TB unlikely)
  - AFB smear negative: sensitivity 66%, specificity 98% (i.e., AFB smear negative, but intermediate – high clinical suspicion, NAAT positive → TB!)
NAAT: Summary

- The test characteristics of NAAT are variable depending on the AFB smear results and clinical suspicion.
  - High suspicion → positive NAAT confirms TB
  - Smear positive, low suspicion (NTM suspected) → negative NAAT supports NTM diagnosis
  - When AFB smear is negative and clinical suspicion is low, don’t use NAAT because of ↑ false-positive

Rapid Molecular Drug Susceptibility Testing for Rifampin

**Guidelines**

*strong recommendation, moderate-quality evidence*

- Either AFB smear positive or NAAT positive AND one of the following criteria:
  1) TB Treatment in the past
  2) Born in or has lived for at least 1 year in a country with at least a moderate TB incidence (≥20 per 100 000) or a high primary MDR-TB prevalence (≥2%)
  3) Contacts of MDR-TB
  4) HIV infected
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**
  - Positive TST or IGRA, AND
  - Compatible signs/symptoms/imaging findings, AND
  - Response to treatment with $\geq 2$ drugs, AND
  - Completed full diagnostic evaluation

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**Diagnostic Criteria in the U.S.**

- Positive smear: 1%
- Positive NAA: 2%
- Clinical case definition: 15%
- [CATEGORY NAME]: 5%
- [CATEGORY NAME]: 77%

CDC 2016
### Approach to the smear-positive patient when NAAT was not performed

- **High clinical suspicion:**
  - Isolation, empiric TB treatment, NAAT

- **Low clinical suspicion:**
  - Request NAAT (still consider possible isolation and empiric TB treatment unless NTM is very likely)

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### 40 yo homeless man

- Lives in a homeless shelter
- Cough x one month

Sputum AFB smear positive
NAAT was not ordered

Your plan?
75 yo woman

- Lives with her husband in a rural area
- Cough x one month

Sputum AFB smear positive
NAAT was not ordered

Your plan?

Low Uncertain/Unclear
No Rx
Wait for Final ID

Uncertain/Unclear
Consider Rx if benefits>risks
1. Risk of progression
2. Risk of transmission
3. Risk of adverse effects

High
Initiate Rx
If no response (or worsening)

Re-assess for other diagnoses when ID is still pending
1. Repeat or additional Imaging (e.g., CT)
2. Obtain tissue biopsy for culture and pathology
Is this TB?

50 yo man with COPD
• 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…

▪ Isolation
▪ Initiation of empirical TB treatment
▪ 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
- High-profile investigations

Diagnostic Process: Other consideration

- Pulmonary vs. extrapulmonary
- Community risk (environment where the patient spends his/her time)
Summary

- Wide range of clinical TB presentation
  - Different levels of public health implication
- Presumptive treatment based on infectiousness, environment, and severity of illness
- Communication with TB labs is critical