Clinical Presentation and Diagnosis of Tuberculosis

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Diagnosis of Tuberculosis

Overview:
- Fundamental principles of TB diagnosis
- Clinical presentation of TB disease
- Laboratory diagnosis of TB disease
  - Sputum smears, culture, nucleic acid amplification tests (NAAT)
- Approach to patients suspected of having TB

ARS: Question 1
In the past year, I have diagnosed or cared for:

A. 0-5 active TB cases
B. 5-10 active TB cases
C. 10-20 active TB cases
D. >20 active TB cases

[Bar chart showing percentages for A, B, C, D]
TB or Not TB?: Case 1

- 57 year old African-American man found staggering and incoherent
- Complains of tongue pain and 50 lb weight loss
- Exam: Afebrile, cachectic, disoriented, enlarged and ulcerated tongue
- Lab: Na - 125, WBC 13.6

ARS: Question 2
In the SFGH Emergency Room:

A. TB is high in my ddx
B. TB is a consideration because of the weight loss and low Na
C. I doubt I would be thinking of TB with this initial presentation

Case 1: Are you thinking TB now?
Diagnosis of Tuberculosis

Fundamental Principles:
- Rapid, accurate diagnosis is essential for individual and public health
- Definitive diagnosis requires isolation of *M. tb* or identification of specific DNA; may also diagnose based on clinical case criteria
- But key point…..

Despite technical advances, clinical acumen with a *high index of suspicion* remains vital to the diagnosis of tuberculosis.

Think TB

Clinical presentation of TB disease
- CDC case definitions
- Risk factors
- Signs and symptoms
- Radiographic presentation
TB Diagnosis: CDC Case Definition (2009 update)

- **Clinical Case Definition**
  - Positive tuberculin skin test or IGRA
  - Signs and symptoms compatible with TB
  - Treatment with two or more anti-TB drugs [clin. response]
  - Completed diagnostic evaluation

- **Laboratory Criteria for Diagnosis**
  - Isolation of Mtb by culture or demonstrate Mtb by NAAT
  - Or demonstrate AFB smear + (if cx not obtained)

- **Confirmed Case**: a case that meets the clinical case definition or is laboratory confirmed

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TB Diagnosis: CDC Reported Cases

Reported TB Cases by Verification Criterion United States, 2014

- Provider diagnosis 9%
- Clinical case 16%
- NAAT 2%
- Culture positive 77%

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Suspicion

For TB

Start by asking

- Any TB risk factors?
TB Diagnosis: Risk Factors
Must THINK TB \(\Rightarrow\) consider dx in High-risk groups

- HIV / Immunosuppressed
  - (chemotherapy, steroids, TNF-alpha inhibitors)
- Foreign-born from high prevalence areas
- TB contacts
- CXR suggestive of prior TB disease
- Predisposing medical conditions
  - (ex. DM, silicosis, hematologic/head-neck malignancies, etc)
- Substance abuse, homeless, jails, tobacco
- Healthcare workers, institutional residence

Suspicion
For TB

Start by asking
- Any TB risk factors?
- Any symptoms suggestive of TB?

“Classic” TB Clinical Presentation

- Insidious onset, chronic course
- Chest symptoms
  - Cough (usually productive)
  - Hemoptysis
  - Chest pain (usually pleuritic)
- Nonspecific constitutional symptoms
- Extrapulmonary symptoms
Clinical Presentation: Signs and symptoms

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

Barnes 1988, Miller 2000

Clinical Presentation of TB

Remember: TB can be tricky

- TB can involve any organ or tissue
- Symptoms severity: none to overwhelming
- Tempo of illness: ranges indolent to fast
- Symptoms/findings: both local and systemic
- Presentation may be atypical in HIV or immunocompromised; diabetes
- TST or IGRA results do not make or break diagnosis of active TB

Clinical Presentation: Site of Disease

CDC Reported TB Cases by Form of Disease United States, 2014

- Pulmonary (69%)
- Lymphatic (38%)
- Pleural (16%)
- Peritoneal (6%)
- Genitourinary (5%)
- Meningeal (5%)
- Bone/joint (10%)
- Other (20%)
- Extrapulmonary (21%)
- Both (10%)
Start by asking:
- Any TB risk factors?
- Any symptoms suggestive of TB?
- CXR suggestive of TB?

“Typical”/ Reactivation TB

1° TB: Adenitis and consolidation

Courtesy M. Gotway, MD
Radiographic Patterns: Pulmonary TB

<table>
<thead>
<tr>
<th>TB Pattern</th>
<th>&quot;Typical&quot;/ Reactivation</th>
<th>&quot;Atypical&quot;/ Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrate</td>
<td>85% upper</td>
<td>Upper:Lower 60:40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usually upper in children</td>
</tr>
<tr>
<td>Cavitation</td>
<td>Often present</td>
<td>Rare</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>Rare</td>
<td>Children common: Adults ~30% Unilateral &gt; bilateral</td>
</tr>
<tr>
<td>Effusion</td>
<td>May be present</td>
<td>May be present</td>
</tr>
<tr>
<td>HIV</td>
<td>CD4 &gt;200</td>
<td>CD4 &lt;200</td>
</tr>
</tbody>
</table>

TB or not TB?

Start by asking:
- Any TB risk factors?
- Any symptoms suggestive of TB?
- CXR suggestive of TB?
- Yes → Lab confirmation
Laboratory diagnosis of TB

- Sputum AFB smear and culture
- Nucleic acid amplification tests (NAAT)
  - Smear positive and negative cases
- Rapid Molecular Tests

Sputum Examination

- AFB smears
  - Rapid (minutes), ~70% sensitive, population-variable specificity
- Culture and speciation
  - Slow (days for liquid media, weeks for solid media)
  - Sensitive (but “culture-negative” cases) and specific
- Nucleic acid amplification tests
  - Rapid (hours)
  - Sensitivity greater than smear, less than culture
  - Specificity depends on quality of lab
  - Can sometimes also detect drug resistance

Collection of Respiratory Specimens

- Sputum Expectoration:
  - 2-3 specimens (at least 8 hours apart)
  - Spontaneous morning specimens best
- Sputum Induction: if non-productive
- Bronchoscopy: if alternative diagnoses are a substantial concern
  - Post-bronchoscopy sputum
Performance of Sputum Microscopy

<table>
<thead>
<tr>
<th>Specimen Number</th>
<th>Incremental Yield (of all smear positive)</th>
<th>Incremental Sensitivity (of all culture positive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>85.8%</td>
<td>53.8%</td>
</tr>
<tr>
<td>2</td>
<td>11.9%</td>
<td>11.1%</td>
</tr>
<tr>
<td>3</td>
<td>2.4%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>68.0%</td>
</tr>
</tbody>
</table>

Average yield of single early morning specimen: 86.4%
Average yield of single spot specimen: 73.9%


TB or not TB?

66 yo male from Philippines
- 6 weeks productive cough and fatigue
- 18 lb. wt. loss

Smear-negative x3
△ is this TB?

Laboratory Diagnosis: Sputum AFB Smear

- Smear positive = at least 10^4 bacilli per ml
- Smear positivity correlates with contagiousness
- Primary determinant of +smear is extent of disease
- Do 3 negative smears “rule-out TB”?  
  - 40-60% of culture-positive cases will be smear negative
  - 21% of US cases (2014) were culture negative
- Clinical pearl: in patients with cavities/extensive disease on chest x-ray whose smears are negative, begin to look aggressively for alternative non-TB dx!
TB or not TB?

48 yo male with COPD
- 1 month cough
- Jail inmate
- Rx MAC two years ago

Smear-positive, is this TB?

ARS: Question 3
Start 4-drug TB treatment?

1. Yes
2. No

ARS: Question 4
Begin large-scale contact screening of 250 inmates and staff?

1. Yes
2. No
Laboratory Diagnosis: Predictive value of a positive smear

- Smear positive for AFB
- Culture and Speciation
- M. tuberculosis
  - 50-90%
- Non-tuberculous mycobacteria
  - 10-50%

Predictive value of a positive smear is reduced in populations with increased prevalence of non-tuberculous mycobacterial infection.

Laboratory Diagnosis: Culture

- Cultures may take several weeks for results
- May get earlier results with liquid media

<table>
<thead>
<tr>
<th>Culture media</th>
<th>Time to Positive Culture</th>
</tr>
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<tbody>
<tr>
<td>Egg-based media (e.g. Lowenstein-Jensen)</td>
<td>4-8 wks</td>
</tr>
<tr>
<td>Agar-based media (e.g. Middlebrook 7H10)</td>
<td>4-6 wks</td>
</tr>
<tr>
<td>BACTEC liquid medium</td>
<td>2-4 wks</td>
</tr>
<tr>
<td>Mycobacterial growth indicator tube (MGIT)</td>
<td>2-4 wks</td>
</tr>
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ARS: Question 5
Would you order a NAAT?

1. Yes
2. No, don’t need test
3. No, not available
4. Don’t know what this is
Laboratory Diagnosis: Nucleic Acid Amplification Tests (NAAT)

- 3 direct amplification tests FDA-approved
  - Gen-Probe/MTD and Xpert Mtb/RIF
  - (Roche Amplicor no longer available in US)

- Use directly on specimen, result < 1 day
  - Best for smear+ (approved for smear-)
  - No current TB rx >7 days
  - No prior TB rx within past 12 months

Usefulness of test in making diagnosis of TB depends on degree of clinical suspicion

Laboratory Diagnosis: Approaches to Using NAAT

Patient with smear-positive specimen

<table>
<thead>
<tr>
<th>NAAT</th>
<th>Positive NAAT</th>
<th>Negative NAAT</th>
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<tbody>
<tr>
<td>MTB</td>
<td>≥97%</td>
<td></td>
</tr>
<tr>
<td>NTM</td>
<td>&lt;3%</td>
<td></td>
</tr>
<tr>
<td>MTB</td>
<td>1-8%</td>
<td></td>
</tr>
<tr>
<td>NTM</td>
<td>92-99%</td>
<td></td>
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</tbody>
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- 2009 CDC Guidelines: Test all AFB+/NAAT- specimens for inhibitors
  - Probably not necessary if using Xpert, which tests for PCR inhibitors

TB or not TB? Case 3

48 yo male with COPD
- 1 month cough, wt. loss
- Jail inmate
- Rx MAC two years ago

What if he was smear-negative instead?
**Laboratory Diagnosis: NAAT in Sputum Smear Negatives**

**High Clinical Suspicion**
- Perform NAAT
- Positive NAAT:
  - MTB: 90%
  - Not MTB: 10%
- Negative NAAT:
  - MTB: 5%
  - NTM: 95%

*2009 CDC Guidelines: Consider repeat test for confirmation if AFB-, NAAT+*  
*May not be necessary if using Xpert, given high specificity and low risk of cross-contamination*

**Low Clinical Suspicion**
- Perform NAAT
- Positive NAAT:
  - MTB: 20%
  - Not MTB: 80%
- Negative NAAT:
  - MTB: <1%
  - Not MTB: 99%

*2009 CDC Guidelines: Avoid NAAT in this clinical scenario*  
*Same holds true for Xpert, which provides no added value over smear*

**CDC: MMWR** January 16, 2009/58(01);7-10

*Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis*

“...CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test would alter case management or TB control activities, such as contact investigations”
TB or not TB?

Actually, real case:
- 20 yo from Mongolia
- 1 month cough, wt. loss
- Smear +

Concern for MDR?

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**TUBERCULOSIS DIAGNOSTICS**

**Xpert MTB/RIF Test**

**WHO ENDORSEMENT AND RECOMMENDATIONS**

- The Xpert MTB/RIF assay uses real-time PCR, is a highly automated diagnostic microbiological test, it has the potential to revolutionize and transform TB care and control. The test:
  - simultaneously detects TB and rifampin drug resistance which is a common problem for MDR-TB
  - provides accurate results in less than two hours so that patients can be offered proper treatment on the same day
  - has minimal bio-safety requirements, training, and can be housed in non-specialized laboratories

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**Xpert MTB/RIF Test Performance**

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<tr>
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<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Smear pos. TB</td>
<td>95-98%</td>
<td>99%</td>
</tr>
<tr>
<td>Smear neg. TB</td>
<td>60-72%</td>
<td></td>
</tr>
<tr>
<td>Rifampin “R”</td>
<td>98-99%</td>
<td>99-100%</td>
</tr>
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Rapid molecular tests: Drug-resistance

- Drug Resistance Screening by Sequencing (DRSS) Washington State Lab
  - INH (katG, inhA); RIF(rpoB); PZA (pncA)
- Pyrosequencing (replaced Molecular beacons): Amplify target by PCR, "Sequencing by synthesis"; 4-5 hrs from DNA extraction to PSQ results - California State Lab
  - INH (katG, inhA); RIF(rpoB); FQ (gyrA); Injectable (rrs)
- CDC Molecular Detection of Drug Resistance (MDDR) program (above drugs plus ethambutol)

TB or not TB?

- Actually, real case:
  - 20 yo from Mongolia
  - 1 month cough, wt. loss
  - Smear +
  - Concern for MDR?
- Rapid molecular test negative for INH or Rif resistance
- Started RIPE
- Close contacts on INH
- Confirmed Pansensitive

Approach to a Patient Suspected of Having TB
**Approach to a Patient Suspected of Having TB: AFB Smear Positive**

- AFB smear-positive
  - Determine clinical suspicion, If high or moderate
  - Start TB treatment (order NAAT)
  - Culture/speciate (2 to 6 weeks)
  - M. *tuberculosis* (MTB) OR NTM
  - Continue treatment OR Adjust or stop treatment

**Approach to a Patient Suspected of Having TB: AFB Smear Negative**

- Smear negative for AFB
  - Low
    - No Rx, wait for culture result
  - Moderate
    - Assess risk vs. benefit: clinical/immune status, risk of transmission, side-effects of Rx
  - High
    - Initiate Rx
    - If no rx response or progression

**Diagnosis of Tuberculosis: Summary**

- Think TB if “high-risk” profile
  - While lungs are primary site of infection, remember that TB can involve any organ
  - Positive smears correlate to transmission risk and extent of disease, but are negative in half of all cases
  - 21% of U.S. cases are culture negative
  - New (rapid) diagnostic tests available – use wisely
  - Clinical suspicion remains key to diagnosis

The End!