Tuberculosis
Clinical Presentation & Diagnosis

Tuberculosis Clinical Intensive
Wednesday, June 3, 2015
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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%
- No symptoms 10-20%

Source: Barnes 1988, Miller 2000

Clinical Presentation: Site of Disease

CDC Reported TB Cases by Form of Disease United States, 2010

- Pulmonary (68%)
- Lymphatic (40%)
- Extrapulmonary (22%)
- Pleural (16%)
- Bone/joint (10%)
- Genitourinary (5%)
- Peritoneal (5%)
- Meningeal (6%)
- Other (18%)
- Both (10%)
Differential Diagnosis

- Community acquired pneumonia
- Malignancy
- Lung abscess
- Non-TB mycobacteria
- Fungal infection
- Parasite (e.g., paragonimiasis)
- Sarcoidosis
- Rheumatologic disease (e.g., Granulomatosis with polyangiitis, RA)
- Other systemic infections (e.g. brucellosis, melioidosis, relapsing fever, etc.)

Radiographic Patterns: Pulmonary TB

<table>
<thead>
<tr>
<th>TB Pattern</th>
<th>“Typical”/ Reactivation</th>
<th>“Atypical”/ Primary</th>
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<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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults ~30%</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>
<tr>
<td>HIV</td>
<td>CD4 &gt;200</td>
<td>CD4 &lt;200</td>
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</table>
Radiographic Findings EPTB

- Lympadenopathy with central attenuation, septation (neck, chest, abdomen, pelvis)
- Effusions
- Diskitis osteomyelitis +/- paraspinous abscess
- Enhancement of meninges, peritoneum, pericardium
- Ring enhancing CNS lesions
- Omental stranding, mesenteric adenopathy
- Bowel wall thickening +/- abscess
- Urinary collecting system obstruction +/- renal parenchymal destruction
- Adnexal mass
Baseline Diagnostic Examinations for TB (1)

- Imaging
- Sputum (if imaging suggests TB or if immunosuppressed)
  - 1 spot and 2 consecutive first-morning specimens
  - Acid-fast bacillus (AFB) smear-and-culture x3
  - Nucleic acid amplification testing (NAAT) x1-2
- Drug susceptibility testing
  - Molecular (rpoB, katG, inhA, pncA, gyrA, etc.)
  - Culture/MGIT/plates

Baseline Diagnostic Examinations for TB (2)

- Extrapulmonary specimens
  - Chemistry, cell count and cytology on fluids
  - Routine pathology on tissues
  - AFB stain/smear and culture
  - NAAT on sputum, BAL, other fluids and unfixed tissues
  - ADA on pleural and peritoneal fluid??
    - Negative predictive value better than positive predictive value

Additional Examinations in Evaluation for Active TB

- TST?? IGRA??
- HIV serology
- CBC/DIFF
  - Anemia (microcytic>normocytic>macrocytic)
  - Thrombocytosis
- CMP
  - Low albumin
- ESR, CRP
Collection of Respiratory Specimens

- Sputum Expectoration:
  - 3 specimens (at least 8 hours apart)
  - 1 spot specimen (induce prn)
  - 2 consecutive first-morning specimens
- Gastric Aspiration
- Bronchoscopy
- Post-bronchoscopy sputum

Role of the 3rd Sputum Specimen

<table>
<thead>
<tr>
<th>Specimen Number</th>
<th>Incremental Yield (of all smear positive)</th>
<th>Incremental Sensitivity (of all culture positive)</th>
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</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>
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</table>

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


AFB smear-negative TB

- Up to 50% of TB cases are AFB smear-negative
- AFB smear results are an indicator of bacillary load and infectiousness, but negative smears to not exclude disease nor contagiousness
- Consider smear results in the overall context of evaluation, but do not “rule out” TB with negative smears when the clinical suspicion for TB is high.
Bronchoscopy Indications

- Unable to obtain specimen via induction or gastric aspirate
- Sputum smear/PCR negative but clinical suspicion of TB still high
- Sputum smear negative and MDR is a high concern
- Malignancy is suspected

Post-Bronchoscopy Sputum

- 57 sputum smear-negative or non-productive\(^1\)
  - 33% AFB smear-positive PBS
  - 7% PBS sole culture-positive specimen
- 56 culture-confirmed cases with negative sputum AFB smears or non-productive\(^2\)
  - AFB smear sensitivity:
    - BAL 57%
    - PBS 77%
    - BAL + PBS 84%


Collection of Other Specimens

- Thoracentesis/paracentesis/lumbar puncture
- Fine needle aspirate (cervical LN)
- Pleural/peritoneal biopsy
- CT-guided needle (chest mass, psoas abscess)
- Video-assisted thoracoscopic surgery
- Mediastinoscopy
- Excision/debridement (LN, bone/joint)
Pleural TB Specimens

- Respiratory (sputum, BAL)
- Pleural fluid
- Pleural biopsy

Typical Findings Extrapulmonary Specimens

- Protein elevated
  - Pleural/peritoneal (>4-5gm/dL)
  - CSF (>100-500mg/dL)
- Moderately decreased glucose (~40-50mg/dL)
- Pleocytosis
  - Pleural (500-5,000 WBC/μL)
  - CSF (100-500/μL)
- Lymphocyte predominant differential
- Necrotizing granulomata
- NAAT 50-75%
- AFB smear: 10-50% AFB culture: 60-90%

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.
Nucleic Acid Amplification Tests (NAAT)

- Varieties
  - Amplified MTD (GenProbe)
  - GeneXpert Mtb/RIF (Cepheid)
  - Non FDA Approved
    - MTBDR Plus (Hain)
    - Others
  - Laboratory developed
- Use
  - Directly on processed specimen
  - No current TB rx >7 days
  - No prior TB rx within past 12 months

Xpert MTB/RIF Test Performance for Diagnosis of Pulmonary TB

<table>
<thead>
<tr>
<th></th>
<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>
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<tr>
<td>Rifampin “R”</td>
<td>98-99%</td>
<td>99-100%</td>
</tr>
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Laboratory Diagnosis: Approaches to Using NAAT

Patient with **smear-positive** specimen

- **NAAT**
  - Positive NAAT
    - MTB ≥97%
  - Negative NAAT
    - NTM <3%
    - MTB 1-8%
    - NTM 92-99%

2009 CDC Guidelines: Test all AFB+/NAAT- specimens for inhibitors

- Probably not necessary if using Xpert, which tests for PCR inhibitors
NAAT Performance
Sputum Smear Negative

High Clinical Suspicion (e.g., 50% pre-test probability)

- Perform NAAT
  - Positive NAAT: MTB ≥90%, Not MTB 10%
  - Negative NAAT: MTB 25%, Not TB 75%

*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.

NAAT Performance
Sputum Smear Negatives

Low Clinical Suspicion; e.g., 5% pre-test probability

- 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.

Molecular Drug Susceptibility Testing
Detection of Common Resistance Conferring Mutations

- Requirements: sufficient DNA (smear positive sputum or culture growth)
- Time to results: ~1 week
- Target sequences: rpoB, katG, inhA, others
  - Xpert MTB-RIF (rpoB only)
  - Hain GenoType MDRTB-Plus (rpoB, inhA, katG)
  - WA DOH TB Lab (rpoB, katG, inhA, pncA)
  - CDC (all of the above, gyrA, emb, [injectables])
Molecular Drug Susceptibility Testing
Typical Indications
• Treatment failure
• Previous treatment for active TB
• Known contact to confirmed case of MDR
• From a highly MDR-endemic setting (e.g., S. Africa, Baltic states, Russian prison)

Culture-negative TB
Diagnostic Criteria
• Compatible clinical and radiographic syndrome
• AFB cultures negative
  – 10-15% pulmonary
  – 25-30% extrapulmonary
• Clinical/radiographic improvement on therapy
• Other causes reasonably excluded
• Positive TST-or-IGRA

Latent TB Diagnosis
Latent TB
Diagnostic Criteria
- No symptoms suggestive of TB
- Epidemiologic risk for acquisition
- Positive IGRA-or-TST
- Normal PA CXR (PA/LAT if <5 y/o)
- CDC/ATS Class 2

Old, Inactive TB
Diagnostic Criteria
- No symptoms suggestive of TB
- Compatible chest radiograph
  - Upper zone fibrotic, fibronodular, or fibrocalcific opacities
  - Volume loss/retration
- Positive IGRA-or-TST
- Negative sputum AFB smears and cultures
- Follow-up CXR stable
- CDC/ATS Class 4

Cases
Case 1 Clinical Presentation

- Cough, chest pain, fever, anorexia x 6 weeks
- What is your next step?

Case 1: Chest Radiographs
2007 vs 2013

Case 1—Evaluation

- Sputum AFB smears 1+ on 2 separate specimens
- What else?
Case 1: NAAT

- Positive for MTB
- Negative for MAC

Case 2—Clinical Presentation

- 33 y/o Amharic-Ethiopian male
- Visited home recently for 3 months
- Malaise, fatigue, fever x 1 month
- Left chest pain worsening over past 2-3 weeks
- Weight 63kg → 60kg
- T 38.5°C; left base dull to percussion with decreased breath sounds

Case 2—Chest Radiograph

[Image of chest radiograph]
Case 2—Initial Evaluation

- HIV negative
- Hgb 10, MCV 80, albumin 3.1
- TST placed

Case 2—Pleural Fluid

- Protein 4.4 gm/dL,
- WBC ~1500 (65% lymphocytes)
- No AFB seen
- Pleural biopsy: necrotizing granulomata without visible AFB (culture pending, PCR not done)
- TST 18mm

Case 2—Week 4 Chest Radiograph

Diagnosis after thoracentesis  After 4-Weeks Rx
Questions? Comments?

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