Clinical Presentation and Diagnosis of Tuberculosis

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Oakland CA, September 14, 2016
Slides adapted from Lisa Chen, MD

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
  - Empirical treatment before or without confirmation

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: AFeverile, cachectic, disoriented, enlarged and ulcerated tongue
- Lab: Na - 125, WBC 13.6
TB or Not TB?: Case 1 risk factors

Exposure factors
- African-American - US born
- Homeless

Progression risk
- Substance abuse, HIV

Clinically compatible
- TB symptoms, signs, laboratory results
- Radiologic abnormalities

Case 2: 19 y.o. woman in emergency department – TB case or not?
- Nepalese arrival 6 mo. ago, no hx of TB or TST
- Fever and abdominal pain
- UA: pyuria, hematuria
- CXR "no evidence of TB"
- Rx: ciprofloxacin
- Did not keep follow-up appt.

Case 2: 19 y.o. woman in ED after 6 mo.
- Sudden onset of severe abdominal pain
- Negative past medical history except for UTI 6 months earlier
- No known TB exposure, no prior TST
- X-ray ➔
Case 2: 19 y.o. woman in ED

- Perforated colon at laparotomy
- Granulomatous inflammation
- Sputum AFB smear +
- Expired despite I.V. levofloxacin, amikacin, rifampin & antibiotics

News Alerts

Colorado Springs Student From Nepal Dies From TB Woman Was International Student At CSU-Pueblo

POSTED: 1:16 pm MDT June 11, 2007

COLORADO SPRINGS, Colo. — Tuberculosis was confirmed as the cause of death of a patient who died at Colorado Springs' Memorial Hospital shortly after arriving at the emergency room on Friday.

It was not known what type of TB killed the 19-year-old student from Nepal but officials held an afternoon news conference to discuss the case.

Collins J. Student TB. Ann Thor Soc 2016

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

Verified CDC TB Case Definition (2009 update)

- **Laboratory Confirmed Case**
  - Positive culture for *M. tuberculosis* complex **OR**
  - Positive NAAT **OR**
  - Positive AFB smear if cx not obtained or possibly false (-)

- **Clinically Confirmed Case**
  - Positive tuberculin skin test or IGRA **AND**
  - Compatible signs & symptoms or clinical evidence of TB **AND**
  - Treatment with ≥ 2 anti-TB drugs **AND**
  - Completed diagnostic evaluation

- **Provider Diagnosed Case**: a case not meeting laboratory **OR** clinical case definitions **may** be reported “as verified”
TB Diagnosis: CDC Reported Cases

Reported TB Cases by Verification Criterion United States, 2014

- Culture positive: 77%
- Clinical case: 16%
- Provider diagnosis: 5%
- NAAT: 2%

Start by asking

- Any TB risk factors?

Suspicion For TB

TB Diagnosis: Risk Factors

Must THINK TB ➔ consider dx in High-risk groups

Exposure risk factors

- TB contacts
- Congregate settings – incarcerated, homeless, substance treatment
- Birth and/or residence in most countries in Asia, Africa, Mexico, Latin America

Progression risk factors

- Immuno-deficiency: HIV, chemo, steroids, TNF-alpha inhibitors
- CXR suggestive of prior TB disease
- Predisposing medical conditions: DM, smoking, silicosis, hematologic/head-neck malignancies, etc
Suspicion
For TB

Start by asking
 Disorder

- 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%
- Nightsweats 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%)
- Extrapulmonary (21%)
- Both (10%)
- Lymphatic (38%)
- Pleural (16%)
- Other (20%)
- Bone/joint (10%)
- Genitourinary (5%)
- Peritoneal (6%)
- Meningeal (5%)

Suspicion For TB

Start by asking:
- Any TB risk factors – exposure or progression?
- Any symptoms suggestive of TB?
- CXR or other findings suggestive of TB?
** 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>
</table>
| Infiltrate | 85% upper                | Upper:Lower 60:40
|            |                          | Usually upper in children |
| Cavitation | Often present            | Rare                |
| Adenopathy | Rare                     | Children common
|            |                          | Adults ~30%
|            |                          | Unilateral > bilateral |
| Effusion   | May be present           | May be present      |
| HIV        | CD4 >200                 | CD4 <200            |
TB or not TB?

Start by asking:

- Any TB risk factors?
- Any symptoms suggestive of TB?
- CXR suggestive of TB?

- Yes → Lab confirmation

Suspicion For TB

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?

- What factors would you consider for starting active treatment now?

Case 3: 18y/o from Somalia

- An adolescent refugee from Africa moved to Chicago in May '06
- Asymptomatic
- (+) PPD
- (-) HIV

Smear-negative x3
- is this TB?

Case 3: 18y/o from Somalia

- 3 sputa were smear and culture negative
- 2 month CXR was stable
- Still asymptomatic
...So the patient was started on Rifampin for Latent TB

2 mo follow-up
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
  - 67% of culture+ screening-detected cases are 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, the diagnosis may be inactive TB, but strongly consider an alternative non-TB dx!

Case 4: TB or not TB?: 20 y.o. student

TST+ at initial college testing
- Erythromycin for pneumonia 6 mo. ago in Thailand
- Asymptomatic now
- X-ray: normal except left mid-lung zone
- Sputum AFB smear-negative (3)

Case 5: TB or not TB?

48 yo male with COPD
- 1 month cough
- Jail inmate
- Rx MAC two years ago
Smear-positive, is this TB?
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>
</thead>
<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>
</tbody>
</table>

Laboratory Diagnosis: Nucleic Acid Amplification Tests (NAAT)

- 3 direct amplification tests FDA-approved
  - Gen-Probe/MDT 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>MTB Positive</th>
<th>NTM Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTB</td>
<td>≥97%</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>NTM</td>
<td>1-8%</td>
<td>92-99%</td>
</tr>
</tbody>
</table>

- 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 5

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

<table>
<thead>
<tr>
<th>High Clinical Suspicion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform NAAT</td>
</tr>
</tbody>
</table>

Positive NAAT

<table>
<thead>
<tr>
<th>MTB</th>
<th>Not MTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Negative NAAT

<table>
<thead>
<tr>
<th>MTB</th>
<th>NTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>95%</td>
</tr>
</tbody>
</table>
Laboratory diagnosis: NAAT in Sputum Smear Negatives

- 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”

NTCA/APHL consensus April 2016: Use of Xpert in decisions on isolation in HC facilities

Note: In some facilities Xpert is replacing smear for initial onsite sputum testing.
Case 3: 18y/o from Somalia

- Came from Chicago to Denver Public Hlth 2 mo. later
- Asymptomatic
- Took 1 mo. RIF, none for 1 mo.
- Chest X-ray:

What to do now?

Xpert MTB/RIF Test Performance

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<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>
</tbody>
</table>

Rapid molecular tests: Drug-resistance

- Drug Resistance Screening by Sequencing (DRSS)
  Washington State Lab and HAIN assay by some labs
  - 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); Injectables (rrs)
- CDC Molecular Detection of Drug Resistance (MDDR) program (above drugs plus ethambutol)

Approach to a Patient Suspected of Having TB

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

<table>
<thead>
<tr>
<th>AFB smear-positive</th>
<th>Determine clinical suspicion, if high or moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start TB treatment (order NAAT)</td>
</tr>
<tr>
<td></td>
<td>Culture/speciate (2 to 6 weeks)</td>
</tr>
</tbody>
</table>

- *M. tb* Continue treatment
- *NTM* Adjust or stop treatment

Consider holding treatment if NAAT negative?
Reasonable if no risk factors for rapid worsening or transmission, as we await more data
Approach to a Patient Suspected of Having TB: AFB Smear Negative

<table>
<thead>
<tr>
<th>Smear negative for AFB</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rx, wait for culture result</td>
<td>Asses risk vs. benefit: clinical/immune status, risk of transmission, side-effects of Rx</td>
<td>Initiate Rx</td>
<td>If no rx response or progression</td>
</tr>
</tbody>
</table>

Rule-out other diagnosis, may consider use of:
1. Imaging (CT/US)
2. Bronchoscopy/FNA/biopsy (may give additional yield for TB)

Case 3: 18y/o from Somalia
- Sputum AFB-positive
- Patient was started on INH, Rif, PZA, EMB, amikacin, and levofloxacin
- NAA - M. tb & resistance to INH & rifampin detected in 72 hrs
- Cx: M. tuberculosis I/R/Z/E & strep resistant

Who needs a rapid Dx & DST?

Denver experiences:
- Initial diagnosis of AFB + TB in young man from Horn of Africa after Rif for Class 4 TB ➔ MDR
- Previously treated patient from Tibet with AFB smear + pulmonary TB ➔ susceptible
- Initial diagnosis of AFB + TB in young woman from Horn of Africa ➔ MDR
- Young HIV+ man from Egyptian refugee camp with disseminated TB ➔ MDR
Greatest source of delays in DST

At least in Denver:
- Delays in care seeking behavior of patient
- Delays in consideration of TB by provider
- Failure to report patient with suspected, not confirmed TB
- Delays in sputum collection by provider

All these are amendable to improvement by better PH partnership with community members and medical providers

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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!