Tuberculosis

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Faculty Disclosures

- PI for clinical trials with Insmed/Aradigm/Novartis/Chiltern (all bronchiectasis/NTM related)
- Consultant (ended 9/2018)
  - AIT Therapeutics
  - Insmed
Question 1:

A 48-year-old man presents with an posterior segment upper lobe pulmonary infiltrate on the chest radiograph, a positive tuberculin test, and three negative sputum smears.

How should this patient be managed?

a. More sputum smears should be obtained.
b. The patient must have a bronchoscopy for diagnosis.
c. The patient should be empirically treated for TB.
d. The patient does not have TB and should receive INH prophylaxis
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FIG. 3.4
Estimated TB incidence rates, 2016
**FIG. 3.6**
Global trends in the estimated number of incident TB cases and the number of TB deaths (in millions), 2000–2016. Shaded areas represent uncertainty intervals.

**FIG. 3.7**
Countries in the three high-burden country lists for TB, TB/HIV and MDR-TB being used by WHO during the period 2016–2020, and their areas of overlap.
Tuberculosis 2019

- 20 - 40% of patients with active pulmonary TB have negative sputum smears

- Approximately 5,000-10,000 organisms per ml of sputum for AFB positive

- Infecting dose of *M. tuberculosis* can be < 10 organisms

- Empiric therapy may be a reasonable choice when clinical suspicion is high
If diagnostic uncertainty, may consider bronchoscopy
Immediate diagnostic yield in the range of 40%
Contribution of BAL is negligible

Results of Mycobacterial Cultures (23 procedures/22 pts with TB)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Positive specimens</th>
<th>Exclusive Positive specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prebronch sputum collection</td>
<td>14/21 (67%)</td>
<td>6/21 (29%)</td>
</tr>
<tr>
<td>Bronchoscopy procedures</td>
<td>10/23 (44%)</td>
<td>2/23 (9%)</td>
</tr>
<tr>
<td>Bronchial wash</td>
<td>1/23 (4%)</td>
<td>0/23 (0%)</td>
</tr>
<tr>
<td>Transbronchial biopsy</td>
<td>1/5 (20%)</td>
<td>0/5 (0%)</td>
</tr>
<tr>
<td>Postbronchoscopy sputum</td>
<td>8/23 (35%)</td>
<td>2/23 (9%)</td>
</tr>
</tbody>
</table>

Wallace wt al AMJMed 1981
Smear negative does not mean non-infectious

- Behr at al, Lancet 1999 - aimed to estimate the risk of transmission from smear-negative patients

- 1359 culture-proven TB cases with fingerprints

- Of 71 clusters identified, 28 (39%) had a smear negative source

- Smear-negative, culture positive TB responsible for 17% transmission in this cohort
Question 2.

A 53-year-old man with AIDS presents with an upper lobe cavitary infiltrate and mediastinal adenopathy on the chest radiograph.

All sputum smears are negative.

The patient should be started on empiric TB treatment and followed for clinical improvement.

True or False.
Question 2.

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All sputum smears are negative.

The patient should be started on empiric TB treatment and followed for clinical improvement.

True or False.
HIV and TB

- HIV places patients at risk for multiple opportunistic infections, of which TB is most common
- Bronchoscopy is a valuable tool to exclude other diseases
- Other conditions may present with positive sputum such as:
  - Atypical mycobacteria
  - Nocardia
  - Some legionella species
Kennedy et al, Chest 1992; compared the diagnostic yield of bronchoscopy in culture-proven TB

- 67 HIV-infected
- 45 non-HIV-infected

Bronchoscopy provided an early diagnosis of tuberculosis (positive acid-fast smear or granulomata on biopsy) in:
  - 23 (34%) of the HIV-infected
  - 20 (44%) of the non-HIV infected

TBBX provided exclusive TB dx in six (10%) of 59 HIV-infected patients.
HIV-infected patient with mediastinal adenopathy

Harkin TJ et al, AJRCCM 1998
Question 3.

A 62 year old man presents with back pain, a paraspinal mass and an abnormal chest radiograph has several negative sputum smears and a negative TST. Which next step is correct?

a. He probably has a malignancy and should get a total body CT.
b. He does not have TB as both skin test and sputum smears are negative.
c. He should be empirically treated for TB.
d. A biopsy of the paraspinal mass should be done.
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Pott’s Disease

- Should be suspected in patients with back pain, fever, and positive TST, whether or not the radiograph suggests active disease

- Plain radiographs of the spine are of limited utility; CT scan and MRI better sensitivity

- In no suspicion of active TB, closed needle or open surgical biopsy of the vertebral lesion is recommended
Pott’s Disease

- Demonstration of AFB on stained specimens (20-25% of time); positive cultures (80% of time)

- If neurological symptoms, spinal stabilization needed

- Presentation and course are similar in HIV and non HIV-infected
Vertebral destruction involving 2 adjacent vertebrae
Sparing of intervening disc
Disc herniation
Epidural involvement
Paraspinal abscess with thick enhancing rim

Gouliamos et al, Eur Rad, 2001
Question 4.

A 62-year-old heavy smoker is TST positive and presents with back pain and a pleural effusion. The effusion is an exudative, lymphocyte-predominant effusion with a pH of 7.3. The next step should be:

a. A chest tube should be placed with drainage of the pleural space.
b. Repeat thoracentesis should be performed in 24 hours.
c. A pleural biopsy should be performed.
d. The patient should be empirically treated for TB.
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c. A pleural biopsy should be performed.

d. The patient should be empirically treated for TB.
Tuberculous Pleurisy

- Can occur during primary infection or any time as reactivation disease
- Delayed hypersensitivity response to tuberculous protein
- Exudative, lymphocyte-predominant effusion; less than 5% mesothelial cells
- Almost always unilateral and small
Tuberculous Pleurisy

- Up to 1/3 of patients can have a negative TST
- Without RX spontaneous resolution with a high rate of recurrence (65%)
- Pleural fluid cultures positive < 25%
- Pleural biopsy with granuloma in 60%
- Culture of specimen and path yields dx in 90%
Other diagnostic considerations include:

- ADA levels
- PCR,
  - De Wit et al, Tubercle Lung Dis 1992
  - 84 patients
  - 53 had TB pleuritis
  - PCR of fluid positive in only 43 (sensitivity 81%)
  - Specificity only 78%
- Interferon gamma levels
- Thoracoscopy
Question 5.

A 27-year-old Tibetan woman is diagnosed with MDRTB. She is treated with oral Ethionamide, Levofloxacin, Cycloserine and PAS. Her chest radiograph reveals a cavitary right upper lobe infiltrate. Which of the following is true?

a. She should have the diseased lung resected.
b. She should be followed clinically to assess response to therapy.
c. Additional medications should be added even if the isolate is resistant.
d. Serum levels should be checked.
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THE COSTLY BURDEN OF DRUG-RESISTANT TB IN THE U.S.

* The Costly Burden of Drug-Resistant TB in the U.S. Sept 2018, CDC
Global MDR treatment outcomes, 2009-2015

![Bar chart showing MDR/RR-TB cases by year and percentage of cohort for 2012 to 2016. The chart indicates the percentage of treatment success, failure, death, lost to follow-up, not evaluated, and no data reported for each year.](image)
Which Patients are at Risk for Drug Resistant TB?

Birth/residence in country with high incidence of drug resistant TB
U.S. residents who travel to high risk areas
Exposure to patient with relapse or failure

Prior treatment for TB
Treatment failure
Relapse in a patient not on DOT
Poor adherence
Clinical deterioration during 4 drug therapy
Why Do We Have Drug Resistance?

- Inadequate Treatment
  - Incorrect regimen (lack of drugs or knowledge)
  - Poor adherence → Treatment failure relapse with drug resistant TB
    → Transmission of drug resistant TB
"drug-resistant tuberculosis" caused by an isolate of Mycobacterium tuberculosis that is resistant to one of the first-line antituberculosis drugs: isoniazid, rifampin, pyrazinamide, ethambutol, or streptomycin.

Multidrug-resistant tuberculosis (MDR-TB) is caused by an isolate of M. tuberculosis that is resistant to at least isoniazid and rifampin, and possibly additional chemotherapeutic agents.

Extensively drug-resistant tuberculosis (XDR-TB) is caused by an isolate of M. tuberculosis that is resistant to at least isoniazid, rifampin, fluoroquinolones, and either aminoglycosides (amikacin, kanamycin) or capreomycin, or both.

Primary drug resistance is said to occur in a patient who has never received anti-tuberculosis therapy.

Secondary drug resistance refers to the development of resistance during or following chemotherapy in patients who had previously had drug-susceptible tuberculosis.
Multidrug Resistant Tuberculosis (MDR-TB)

Morbidity and mortality is high

- National Jewish experience with second-line drugs of 56% response rate in MDR-TB (defined by negative sputum culture at 3 months) and overall mortality of 37% (Goble, 1993)
- Improved survival of 70% at Bellevue Hospital with early institution of appropriate therapy associated with prolonged survival (Park, 1996)
- Resectional surgery and continued second-line therapy has been associated with cure rates as high as 90% (Pomerantz, 1995)
Surgical Indications for Treatment of Pulmonary Tuberculosis

- Drug resistant TB with failure or relapse
- Bronchiectasis with bronchorrhea, repeated infections, hemoptysis
- Destroyed lung
- Hemoptysis
- Bronchopleural fistula
- Pulmonary aspergilloma
Complications of Surgery for TB

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 80)</th>
<th>Group II (n = 64)</th>
<th>Groups I + II (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BPF</strong></td>
<td>1 (1.25%)</td>
<td>0</td>
<td>1 (0.69%)</td>
</tr>
<tr>
<td><strong>Fluid</strong></td>
<td>32 (40%)</td>
<td>19 (29.7%)</td>
<td>51 (35.4%)</td>
</tr>
<tr>
<td><strong>PTX</strong></td>
<td>9 (11.2%)</td>
<td>3 (4.6%)</td>
<td>12 (8.3%)</td>
</tr>
<tr>
<td><strong>Wound infection</strong></td>
<td>1 (1.35%)</td>
<td>1 (1.56%)</td>
<td>2 (1.39%)</td>
</tr>
<tr>
<td><strong>Morbidity</strong></td>
<td>43 (53.7%)</td>
<td>23 (35.9%)</td>
<td>66 (45.8%)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>0</td>
<td>2 (3.1%)</td>
<td>2 (1.39%)</td>
</tr>
</tbody>
</table>

*a* BPF, broncho-pleural fistula; PTX: Pneumothorax.

Question 6.

A 32-year-old HIV negative woman with pan-sensitive TB is febrile, losing weight, and sputum smear positive despite in hospital treatment for the past month. Possible reasons for this include all of the following except:

a. She is spitting out her medications when the nurse is not looking.
b. She may have malabsorption and drug levels should be sent.
c. She has drug resistant TB.
d. This is a paradoxical reaction to treatment.
Question 6.

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Paradoxical Reaction

- Patient who develop apparent progression of TB while on appropriate treatment may:
  - Not be taking meds (DOT)
  - May be malabsorbing
  - May have drug-resistant tuberculosis
  - May have a paradoxical reaction.
Paradoxical Reaction

- Tissue sites of granulomatous inflammation become clinically apparent or more apparent on therapy
- Most commonly in lymph nodes, brain and lung
- AFB may be present, but culture is usually sterile
- Likely a hypersensitivity reaction to release of TB antigens during therapy
- Seen in both HIV and non-HIV infected patients
- In HIV, has been associated with initiation of anti-retroviral therapy
- Consider corticosteroids in patients with increased intracranial pressure
Complicated Pleural Spaces in TB

- Decortication may be necessary
- Optimal time of decortication remains controversial
- BPF and underlying lung fibrosis/cavitation warrant early surgery
- Pleural drainage and appropriate drug therapy warranted for tuberculous empyema
- In chronic cases with empyema, drug concentrations in pleural space are unreliable (not so in serous Tb pleuritis)
- Lack of parenchymal involvement and BPF predicts re-expansion of trapped lung
Kim et al, J Comput Assist Tomogr 2001
Jouveshomme et al, Am J Respir Crit Care Med 1998
Hemoptysis

- Active TB and bronchiectasis are important causes of hemoptysis
- Rasmussen aneurysm rupture can be cause of massive hemoptysis
- In active TB, treatment of TB usually leads to resolution
- High-resolution chest CT scan can be useful as adjuvant to diagnose and complements FOB
Rasmussen’s Aneurysm

Sanyika et al Cardiovasc Intervent Radiol, 1999
Sanyika et al Cardiovasc Intervent Radiol, 1999
Complications of Embolization

- Spinal Cord syndromes
- Bronchial stenosis
- Broncho-esophageal fistula
- Infarction of the bronchus
- Mediastinal hematoma after subintimal aortic dissection
- Transient cortical blindness
Question 7.

A 65-year-old patient with end stage COPD is admitted with shortness of breath and positive AFB smears. His x-ray shows hyperinflation with no active infiltrates or abnormalities. His last TST was 10 years ago at which time it was positive and he received one year of INH prophylaxis. Which of the following should be done next?

a. The patient should be started on TB treatment.
b. A sputum sample should be sent for PCR.
c. The patients should have a CT scan of the chest.
d. The smear should be repeated because it is probably a false positive.
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PCR and Diagnosis of TB

- The polymerase chain reaction assay can detect DNA from as few as one organism in a variety of biological samples.
- PCR can rapidly confirm that acid-fast organisms belong to the *M. tuberculosis* complex (*M. tuberculosis, M. microti, M. africanum, M. bovs*), and can distinguish these from other mycobacterial species.
Eight-five patients enrolled; 27 were culture positive for TB; 12/27 were smear negative

**TABLE 2**

<table>
<thead>
<tr>
<th>PCR RESULTS</th>
<th>All Tuberculosis (n = 27)</th>
<th>Smear (-) Tuberculosis (n = 15)</th>
<th>Nontuberculosis (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n) (%)</td>
<td>(n) (%)</td>
<td>(n) (%)</td>
</tr>
<tr>
<td>Either of first two in-house (+)†</td>
<td>23 85</td>
<td>11 73</td>
<td>7 12</td>
</tr>
<tr>
<td>Either of first two Roche (+)†</td>
<td>20 74</td>
<td>8 53</td>
<td>4 7</td>
</tr>
<tr>
<td>Both of first two in-house (+)</td>
<td>16 59</td>
<td>4 27</td>
<td>4 7</td>
</tr>
<tr>
<td>Both of first two Roche (+)</td>
<td>13 48</td>
<td>1 7</td>
<td>1 2</td>
</tr>
<tr>
<td>Any of 6 in-house (+)</td>
<td>23 85</td>
<td>11 73</td>
<td>7 12</td>
</tr>
<tr>
<td>Any of 6 Roche (+)</td>
<td>22 81</td>
<td>10 67</td>
<td>4 7</td>
</tr>
</tbody>
</table>

* Includes patients with nontuberculosis mycobacteria.
† p > 0.2 using weighted least-squares method.

**TABLE 4**

<table>
<thead>
<tr>
<th>Incremental Yield of PCR on First Two Specimens</th>
<th>Specimen 1</th>
<th>Specimen 1 or 2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen 1</td>
<td>(n) (%)</td>
<td>(n) (%)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>All tuberculosis, n = 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-house</td>
<td>19</td>
<td>70</td>
</tr>
<tr>
<td>Roche</td>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>Smear-negative tuberculosis, n = 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-house</td>
<td>7</td>
<td>47</td>
</tr>
<tr>
<td>Roche</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Excluding paucibacillary disease, n = 20†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-house</td>
<td>17</td>
<td>85</td>
</tr>
<tr>
<td>Roche</td>
<td>14</td>
<td>70</td>
</tr>
</tbody>
</table>

* If either Specimen 1 or 2 was positive, the patient was considered PCR-positive for this calculation.
† Paucibacillary disease is defined as less than 20 colonies on mycobacterial culture.
Nucleic Acid Amplification (NAA)

- Two nucleic amplification assay currently available: MTD (GenProbe) and Amplicor (Roche)

- NAA should be used to confirm that a positive smear is M. tuberculosis

- If clinical suspicion high, may be done on smear-negative cases (about 50% detected)

- Test cannot replace culture
Question 8.

A hospital employee has converted his skin test and was begun on INH prophylaxis. He developed drug-induced hepatitis and discontinued his treatment. He should?

a. not be offered LTBI treatment
b. be challenged with INH again
c. receive rifampin for 4 months
d. receive PZA/Rifampin for two months
Question 8.

A hospital employee has converted his skin test and was begun on INH prophylaxis. He developed drug-induced hepatitis and discontinued his treatment. He should?

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c. receive rifampin for 4 months
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Targeted testing of populations at high risk with intent to treat

- TST conversion defined as an increase in induration of > 10 mm or Positive interferon gamma release assay (ELISPOT or quantiferon)
- 9 months of INH OR 12 doses of INH/Rifapentine OR 4 months of Rifampin

- History of BCG vaccination should not affect decision to treat
- ** Do not use Rif/PZA alternate due to excess hepatotoxicity reported
Tuberculosis Case rates (%)

• From the Bethel Isoniazid Studies; TB Case rates in the population according to months of INH taken

• Efficacy of INH decreased significantly if less than 9 months of INH were taken

Comstock, Int J Tuberc Lung Dis, 1999
A 32-year-old patient with Hepatitis C and active TB on IRPE develops transaminitis. You should:

a. ignore and continue treatment  
b. stop TB treatment  
c. obtain a liver biopsy to determine if the transaminitis is due to HepC or TB  
d. consider beginning a liver –sparing TB regimen if transaminases are greater than 5x baseline
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Transaminitis in TB

- Level of transaminitis (> 5x baseline) should guide change of therapy as adjustments of regimen have implications for length of treatment
- Hepatitis C transaminitis may fluctuate independent of TB meds
- Consider liver sparing regimen:
  - Aminoglycoside or Capreomycin
  - Ethambutol
  - Cycloserine
  - Quinolone
- May consider re-challenge in selected, monitored cases
Of 146, 32 had transaminitis (>3x)

13 had transaminitis >5x

Development of transaminitis was not associated with hepatitis C or HIV infection

Sadaphal et al, CID, 2001
What to Remember

- Treat empirically in patients with high degree of risk factors
- Need to exclude active disease before starting TB prophylaxis therapy
- Smear negativity does not mean not infectious
- Post-bronchoscopy specimens should be performed in any patient suspect for TB
- TB Pleural disease is often (1/3) ppd negative; resolves on its own (2/3) and often requires pleural tissue for diagnosis
- Latent TB treatment---9 months of INH OR 12 doses of INH/Rifapentine OR 4 months of Rifampin
What to Remember

- PCR should be used to confirm that a positive smear is M. tuberculosis; 50% useful in smear negative specimens.
- PCR alone is not sufficient; always send specimens for culture.
- Asymptomatic trasaminitis is common in patients on standard TB regimens; consider liver sparing regimens when >5x normal.
- Consider surgery as an adjunct to treatment in patients with localized MDRTB disease.
- TB can present in many ways outside the lung; always consider TB in your differential.
Questions?

Special thanks to Dr Rany Condos; Professor of Medicine at New York University/Bellevue Hospital