An Overview of Tuberculosis

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Objectives:

1. Describe 2 risks for TB infection and 2 risks for progression to active TB
2. List the common steps and tests for diagnosing TB
3. Name the first-line medications for treating active TB and common side effects
32 yr old female

- Born in Colorado
- No history of travel
- Was incarcerated in Texas for 4 years, out for about 1 year;
- Presents with c/o sore throat, cough, and fever x 2 weeks
- T 100.2, P 109, BP 114/72  96% on RA
32 yr old female

D/Cd on Azithromycin
32 yr old female

- Returns to ED 2 months later
- Now c/o fever, cough, 50lb wt loss

- T 101.1; BP 114/72
- P 139; 90% on 2L

Smear (+), INH resistant TB
32 yr old female

- Prolonged hospitalization (3mos)
- Rifampin, Pyrazinamide, Ethambutol, Levofloxacin (and Amikacin x 5weeks)

- After 6 mos of therapy, she was readmitted → had a rapid decline and DIED on IV therapy
History of TB

- TB has affected humans for millennia

- Historically known by a variety of names, including:
  - Consumption
  - Wasting disease
  - White plague

- TB was a death sentence for many
History of TB
Scientific Discoveries in 1800s

- Until mid-1800s, many believed TB was hereditary

- 1865 Jean Antoine-Villemin proved TB was contagious

- 1882 Robert Koch discovered *M. tuberculosis*, the bacterium that causes TB
Tuberculosis Epidemiology

~ 2 billion people are infected - A Third of the World!

10% will develop active TB in their lifetime

→ 10 million new active TB / yr
→ 2 million deaths / yr
Reported TB Cases United States, 1982–2009

TB in Colorado: 2001-2010

Cases of Active TB by Year of Report
The Critical First Step –
Consider TB in the Differential

1. Risks for infection or progression
2. Concerning symptoms
3. Fail to respond to standard treatment*
4. Have frequent, unexplained recurrences

* CAUTION fluorquinolones are highly active against TB
Risk Factors for Infection

1. Persons born or lived where TB is common
   Central and South America, Africa, Eastern Europe, Asia and the Pacific Islands

2. Close Contacts to persons with active TB

3. Elderly U.S. born (>70)
Estimated TB incidence rate, 2005

WHO 2006
Colorado’s 85 TB Cases, 2009

60 (71%) Foreign Born – rate 12.3 per 10^5
  • 30 Latin America (26 from Mexico)
  • 20 Asia
  • 9 Africa
  • 1 Europe

Note: 19 different countries

25 (29%) United States – rate 0.6 per 10^5
TB Pathogenesis (1)

Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to small air sacs (alveoli)
Tubercle bacilli multiply in alveoli, where infection begins
A small number of tubercle bacilli enter bloodstream and spread throughout body.
Risk Factors for Progression

- HIV
- Fibrotic CXR c/w prior TB
- Immunosuppression (transplants, TNF-alpha inhibitors)
- Recent close contact to active TB
- Diabetes
- Chronic renal failure
- Silicosis
- Leukemia / lymphoma
- Head/neck cancer
- Wt loss > 10%
- gastric bypass surgery
“Concerning” Symptoms

- General: fever, night-sweats, weight loss, fatigue

- Pulmonary: Cough > 3wks, hemoptysis, shortness of breath, chest pain

- Extrapulmonary - lymphadenopathy, headache, stiff neck, altered mental status, hematuria, chest or abdominal pain etc.
### TB and HIV (1)

<table>
<thead>
<tr>
<th>Symptom/sign</th>
<th>HIV positive (%)</th>
<th>HIV negative (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>97</td>
<td>81</td>
</tr>
<tr>
<td>Fever</td>
<td>79</td>
<td>62</td>
</tr>
<tr>
<td>Sweats</td>
<td>83</td>
<td>64</td>
</tr>
<tr>
<td>Weight loss</td>
<td>89</td>
<td>83</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>35</td>
<td>13</td>
</tr>
</tbody>
</table>
Common Sites of TB Disease

- Lungs
- Pleura
- Central nervous system
- Lymphatic system
- Genitourinary systems
- Bones and joints
- Disseminated (miliary TB)
Cervical Lymphatic & Pulmonary TB
<table>
<thead>
<tr>
<th>Site</th>
<th>HIV positive (%)</th>
<th>HIV negative (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>40</td>
<td>72</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Both</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>Pleural</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Pericardial</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Lymph node</td>
<td>19</td>
<td>3</td>
</tr>
</tbody>
</table>
TB Symptoms (2)

Colorado 2009:

- 73% Pulmonary
- 27% Extrapulmonary (lymphatic, pleural, bone/joint, meningeal, disseminated, peritoneal)

TB tends to be a chronic, indolent disease w/some systemic symptoms …but pts often present reporting an acute illness
AIDS (CD4 2)

Paratracheal and hilar adenopathy
HIV and a CNS Tuberculoma
Medical Evaluation

1. History (including travel)
2. Physical examination (non-specific)
3. Chest x-ray
4. Bacteriologic or histologic examination
5. TB Skin Test (aka TST, PPD) or Interferon-\(\gamma\) Release Assay (IGRA)
25 yr old female

Radiology reading: Fibrotic opacity in the right upper lobe with pleural thickening consistent with scarring from old TB
25 yr old female

- No symptoms
- No past medical history
- HIV (-)
- Sputum AFB smear (-) x 3

Because she has an infant at home, she is started on 4 drug TB therapy

All 3 Sputa were Culture (+) for TB
25 yr old female
41 yr old male

- Born in Mexico, came to U.S. >15 yr ago
- Regular travel back and forth
- Presents to the hospital with cough and DOE for several months
- Known prior (+) TST, never treated
53 year old

- Born in the Pacific Islands
- Known prior (+) TST
- Presented with 1 month of cough, fever, and weight loss
- Refused admission
53 year old

- Hospitalized 2 weeks later
- QFT negative
- Lung bx shows granulomas, AFB smear (-)
53 year old

- 1 month on high dose steroids
Practical Aspects of Diagnosing TB

- The tuberculin skin test (aka TST or PPD) = 70% sensitive

- Blood tests (interferon-\(\gamma\) release assays) = 85-90% sensitive

- Sputum smears = 50% sensitive for pulmonary TB
Interferon-gamma Release Assays

- Blood test for detecting TB infection
- Requires 1 visit (TST requires 2 visits)
- Results less subject to reader bias and error
- More specific with less cross-reaction with non-tuberculosis mycobacterium and BCG than the TST
IGRAs are preferred for:

1. BCG vaccinated
2. Groups with historically low return rates for TST readings
2 Commercially Available IGRAs
QFT-GIT: Sensitivity for Active TB

<table>
<thead>
<tr>
<th>Study, Year [Reference]</th>
<th>Sensitivity (95% CI)</th>
<th>Patients (n/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartu et al. 2008\textsuperscript{15}</td>
<td>0.86 (0.65 - 0.97)</td>
<td>19/20</td>
</tr>
<tr>
<td>Chee et al. 2008\textsuperscript{35}</td>
<td>0.80 (0.75 - 0.85)</td>
<td>224/280</td>
</tr>
<tr>
<td>Detjen et al. 2007\textsuperscript{10}</td>
<td>0.93 (0.76 - 0.99)</td>
<td>26/28</td>
</tr>
<tr>
<td>Dominguez et al. 2008\textsuperscript{28}</td>
<td>0.79 (0.63 - 0.90)</td>
<td>33/42</td>
</tr>
<tr>
<td>Gerogianni et al. 2008\textsuperscript{18}</td>
<td>0.95 (0.75 - 1.00)</td>
<td>19/20</td>
</tr>
<tr>
<td>Harada et al. 2008\textsuperscript{36}</td>
<td>0.87 (0.79 - 0.93)</td>
<td>87/100</td>
</tr>
<tr>
<td>Palazzo et al. 2008\textsuperscript{22}</td>
<td>0.82 (0.57 - 0.96)</td>
<td>14/17</td>
</tr>
<tr>
<td>Aichelburg et al. 2009\textsuperscript{38}</td>
<td>0.91 (0.59 - 1.00)</td>
<td>10/11</td>
</tr>
<tr>
<td>Bianchi et al. 2009\textsuperscript{16}</td>
<td>0.94 (0.70 - 1.00)</td>
<td>15/16</td>
</tr>
<tr>
<td>Kampmann et al. 2009\textsuperscript{25}</td>
<td>0.80 (0.59 - 0.93)</td>
<td>20/25</td>
</tr>
<tr>
<td>Lighter et al. 2009\textsuperscript{40}</td>
<td>0.86 (0.42 - 1.00)</td>
<td>6/7</td>
</tr>
<tr>
<td>Markova et al. 2009\textsuperscript{41}</td>
<td>0.92 (0.64 - 1.00)</td>
<td>12/13</td>
</tr>
<tr>
<td>Sauzullo et al. 2009\textsuperscript{42}</td>
<td>1.00 (0.91 - 1.00)</td>
<td>38/38</td>
</tr>
</tbody>
</table>

Pooled Sensitivity = 0.84 (0.81 to 0.87)
Chi-square = 25.25, d.f. = 12 (p = 0.0137)
Inconsistency (I-square) = 52.5%
T-SPOT.TB: Sensitivity for Active TB

Diel, Chest April 2010 137(4): 952
18y/o male

- Born in Somalia, moved from Chicago
- Empty bottle of rifampin 600 mg, #30 filled at Chicago health dept 2 months earlier
- Says his chest X-ray was abnormal & sputum cultures negative
- Denies any symptoms or signs of TB
Chest X-ray in Denver
Diagnostic Evaluation

- Smears: Neg/Neg/1+
- Fax report from Chicago: 3 negative smears & cultures
- Is this active TB? Is it drug resistant?
## Culture and Susceptibility Testing

<table>
<thead>
<tr>
<th>Method</th>
<th>Time to Detection</th>
<th>Time to Susceptibility</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid Media</td>
<td>3-4 weeks</td>
<td>3-4 weeks</td>
<td>Gold standard</td>
</tr>
<tr>
<td>Broth</td>
<td>10-14 d</td>
<td>5-10 days</td>
<td></td>
</tr>
<tr>
<td>Molecular</td>
<td>1 day</td>
<td>1 day</td>
<td>Newer technologies are making this more feasible</td>
</tr>
</tbody>
</table>
Newer Molecular Tests for Early Detection of Drug Resistant TB

MTBDR – Hain Assay
- Performed on direct specimens (smear +)
- Results in 4-5 hours
- Detects
  - INH and Rifampin
  - Option to test EMB, FQ, Ami/Kana/Capreo
- Requires a specialized lab

J Clin Micro Aug 2010; 48 (8): 2934
Newer Molecular Tests for Early Detection of Drug Resistant TB

Cepheid – GeneXpert

- Performed on direct specimens
- Detects Rifampin resistance
- Automated so requires much less lab capabilities

NEJM Sept 2010; 363: 1005
<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5mg/kg (max 300mg)</td>
<td>Fatigue, peripheral neuropathy, hepatitis</td>
</tr>
<tr>
<td>Rifampin</td>
<td>10mg/kg (max 600mg)</td>
<td>P450 inducer, hepatitis, rash, flu-like sx</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>20-25mg/kg (500mg tabs)</td>
<td>GI upset, rash, hepatitis, ↑ uric acid</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15-20 mg/kg (400mg tabs)</td>
<td>Optic toxicity</td>
</tr>
</tbody>
</table>
Standard Treatment of Tuberculosis

1. Intensive Phase
   - INH, Rifampin, Pyrazinamide and Ethambutol x 2 months
   - First 2 to 3 weeks are spent in home isolation – can’t work, go to school or be out in public places

2. Continuation Phase
   - INH and Rifampin x 4 months
Duration of Therapy

- 6 months – for drug susceptible TB when PZA is included in first 2 months and Rifampin throughout

- Increased risk of relapse with cavitary TB and/or a positive culture at 2 months

- With HIV, increased risk for treatment failure/relapse with low CD4 cell count (< 100)
Directly Observed Therapy

FIGURE 3. Range and median of treatment completion rates by treatment strategy for pulmonary tuberculosis reported in 27 studies

DOT = Directly observed therapy; n = number of studies; Modified DOT = DOT given only for a portion of the treatment period, often while the patient was hospitalized; Enhanced DOT = individualized incentives and enablers were provided in addition to DOT.

18y/o from Somalia

- Confirmed TB resistant to INH and Rif in 72 hours
- Cx (+) MTB resistant to INH, Rifampin, PZA, EMB and streptomycin

Is this XDR-TB?
Drug Resistant Tuberculosis

- **Multi-drug Resistant (MDR)**
  Resistant to at least INH and Rifampin

- **Extensively Drug Resistant (XDR)**
  Resistant to
  - INH and Rifampin plus
  - Fluoroquinolones and at least one second-line injectable agent (amikacin, kanamycin, or capreomycin)
Treatment of Suspected Drug-resistant TB

- Consider when a patient has a prior history of TB treatment and appears to have relapsed
- Consult an expert in TB treatment
- Never add a single drug to a failing regimen (eg. Aminoglycosides or fluoroquinolones)
Contact Information

- Denver Metro TB Clinic  602-7240
- Randall Reves MD (clinic director) 602-7257
- Bob Belknap MD (ID physician) 602-7244
- Denver Public Health 436-7200

CDC Division of TB Elimination - guidelines
http://www.cdc.gov/nchstp/tb/default.htm
Resources

CDC
www.cdc.gov/tb/pubs/mmwr/maj_guide.htm

Francis J Curry Center
www.nationaltbcenter.edu

Stop TB Partnership
www.stobtb.org

WHO
One person dies of TB every 20 seconds. TB is preventable and curable.