Extrapulmonary Tuberculosis

E. Jane Carter, MD
Associate Professor, Brown University
Immediate Past President, The Union

Disclosures

• Grant Funding
  – WHO TB Reach
• Boards
  – Immediate Past President, The Union (Paris, France)
  – Vital Strategies (NYC, NY)
• Contracts
  – Technical Review Panel, Global Fund to Fight AIDS, TB and Malaria
  – USAID- TB Training Grant – Kenya
  – The Union- International Principles of TB Course
• No financial relationship with a commercial entity producing health-care related products and/or services.
## Lecture Outline

- Epidemiology of EP in the US
- Site Specific Cases with Clinical Pearls
  - Lymph Node Disease
  - Bone Disease (Specifically Pott’s Disease)
  - Pleura Disease
- Extra Slides
  - CNS TB
  - Pericardial TB
  - GU TB
  - Xpert in EP TB

## Remember – TB Pathophysiology

- Inspired into the lower lobes
- Scavenged by alveolar mac’s and WBCs
- Phagocytized and packaged into lysosomes
- Trojan horse
  - Carried to lymphatics, systemic circulation
- Over the next few weeks, cell mediated immunity is activated
Pathophysiology

- Organism enters dormant state
  - Anywhere in the body
- Cure can be achieved only through medication use
- Without treatment, 10% risk of developing disease later in life
  - 10% average risk – varies through time and influenced by co-morbidities
- Thus- TB disease can occur anywhere in the body

Definitions

- Pulmonary TB
  - TB Disease in the lung parenchyma
  - Respiratory specimens are the diagnostic specimen of choice
- Extrapulmonary TB
  - TB disease in any organ system other than Pulmonary parenchyma (including pleural TB)
  - The specimen of choice is tissue of whatever body part is involved
  - Paucibacillary disease – often difficult to obtain bacteriologic confirmation
- Disseminated TB
  - Confirmed (B+) TB disease in two or more noncontiguous sites
  - This is usually diagnosed with a patient is very ill - we don’t “stage” all pulmonary patients to see if they have other site disease
- Miliary TB
  - Specific radiologic pattern – represents TB bacteremia
Epidemiology
EP TB in the US

TB Cases by Site of Disease USA – 2015**

- Total cases: 9,421
  - Pulmonary TB: 6,491
  - Extra-pulmonary TB: 1,938
  - Both Pulm & E-P TB: 978

E-P rates are higher in non-US-born

** Latest year for which there is available data by site of disease.
Extrapulmonary (E-P) TB in USA – 2015**

1933 E-P* cases in 2015
Many cases with > 1 site

*Excludes those with both pulm/extrapulmonary

<table>
<thead>
<tr>
<th>Site of disease</th>
<th>Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic</td>
<td>715 (35.2%)</td>
</tr>
<tr>
<td>Pleural</td>
<td>349 (17.2%)</td>
</tr>
<tr>
<td>Bone &amp; Joint</td>
<td>196 (9.6%)</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>126 (6.2%)</td>
</tr>
<tr>
<td>Meningeal</td>
<td>91 (4.5%)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>92 (4.5%)</td>
</tr>
<tr>
<td>Laryngeal</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td>Other</td>
<td>459 (22.6%)</td>
</tr>
</tbody>
</table>


** Latest year for which there is available data by site of disease.

Trends in EPTB and PTB; 1993-2006
Risks Factors for E-P vs Pulmonary TB

- Human immunodeficiency virus (HIV)
- Female gender (LN, CNS, Bone & Joint)
- Age (lowest 0-14 y)
- End-stage renal disease
- Non-smokers
- Longer interval from contact to disease
- Not associated with MDR, incarceration, alcoholism, homelessness (US)

Extrapulmonary TB: Site Predilection

- Meningeal and lymph node TB seen frequently in children
- GU and bone/joint in older adults
- Meningeal and pleural more commonly seen in US born

Peto, CID, 2009
Fiske, BMC ID, 2010
Pathogenesis of E-P TB

- Hematogenous/lymphatic dissemination
- Some tissues common, others rare
- Increased arterial supply, high O$_2$ content
- Trauma, especially bone/joint TB
- Host immunity: genetics, macrophage capacity

1H.Schaaf & A.Zumla, eds. *Tuberculosis*. 2009

Issues in Selected Sites of E-P TB

- High mortality: CNS, pericardium
- Cosmetic/pressure effect: lymph nodes
- Respiratory component: pleura
- Mobility: bones, joints
- Subtle presentations: abdominal, g-u, pelvic
- Infertility (pelvic/GU)
Cases and Clinical Pearls

Lymph Node Case

40.4% of EP TB
24.6% Cervical
5% Intra-thoracic
10.8% Other/unknown
Case #1

- 62 year old male born in Guatemala presents with an enlarging neck mass
- Mass noted for over 11 months- growing to now cross midline, making it difficult for him to close his shirt collar
- Denies fever, chills, or any infectious symptoms. Does note 15 # weight loss
- Smoker

Case #1

- Referred to ENT for biopsy of his head and neck cancer
- Biopsy #1= No cancer
- Biopsy #2 = No cancer
- Biopsy #3 = No cancer (and pathologist recommended ID consultation due to ongoing appearance of Necrotizing Granuloma on all biopsies)
Case #1

- Father and Aunt had TB when patient lived with them
- TST 35 mm
- CXR Normal
- PE remarkable for large draining surgical wound
- Swab taken of drainage (no cultures sent from surgery)
- Started on IRZE DOT

TB Adenitis
Lymphadenitis with sinus track

Pathophysiology and Treatment

- Oral route of inoculation (drinking unpasturized milk) - particularly in cervical disease
- Hematogenous seeding of the nodes
- Diagnosis:
  - Isolation of TB from specimens (aspirate, surgical biopsy)
  - Combination of epidemiology and smear/histology
- Treatment – No different than your pulmonary case
Clinical Pearls - Lymph Node Disease

• Presentation is generally painless
• Epidemiology is helpful
• Diagnosis made by combination of factors including Smear, Culture, and Epidemiology (TST/IGRA status)
• During treatment it is not uncommon for nodes to enlarge, drain, or other nodes to appear
  – Immunologic basis not a microbiologic failure
  – Warn the patient as well as the HCWs involved

Pleural Disease

19.8% of EPTB
Case #2

- 65 year old male born and living >9 months of the year in Cape Verde
- Fever and cough
- March 2014 – hospital in CV – AB (yes but which one?)
- Come to the US for treatment – May 2014
Case #2 - In patient evaluation

- PE unrevealing other than chest exam
- HIV negative; Routine blood work unrevealing
- Thoracentesis - Exudative, lymphocytic effusion X 2
- Ph 7.43; Glucose 72
- Cytology negative
- ADA 47
- TST ?? Not clearly reported in chart (one note mentioned an 8 mm TST “not significant”)
- Sputa smears and pleural fluid = AFB smear negative
- Pleural fluid all gram stain and culture negative
- Discharged to pulmonary (me!)

Outpatient

- Felt well except mild chest discomfort
- Cough gone
- PE unremarkable
- CXR now normal – no effusion at all
Outpatient

- TST now 55 x 32 mm in size
- Presumptive TB - Started on IRZE DOT

Pathophysiology and Treatment

- Rupture of a granuloma into the pleural space causing a “giant” TST reaction there
- Treatment is similar to pulmonary case in terms of management
- Natural history of TB effusion is to go away
  - But 65% will reactivate with pulmonary disease in the next 2 years
### Diagnostic tests and yields

<table>
<thead>
<tr>
<th>Test</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear fluid</td>
<td>5% Positivity</td>
</tr>
<tr>
<td>Culture of fluid</td>
<td>&lt;40% Positivity</td>
</tr>
<tr>
<td>Pleural biopsy</td>
<td>60-90%</td>
</tr>
<tr>
<td>ADA &gt;45 Units/ml</td>
<td>92% sensitivity and 90% specificity</td>
</tr>
<tr>
<td>NAAT</td>
<td>Low sensitivity (37-60%) and high specificity</td>
</tr>
<tr>
<td>XPert</td>
<td>25% sensitivity 100% specificity</td>
</tr>
</tbody>
</table>

### Clinical Pearls

- An exudative, lymphocytic Effusion without any other explanation in the face of TB infection (+TST/IGRA) should be strongly considered TB and treated empirically.
- Natural history of TB effusion is to go away.
  - But 65% will reactivate with pulmonary disease in the next 2 years (thus very important to treat even if he is found as my case at a time he is recovering).
Bone Disease (specifically Pott’s Disease)

11.3% of EPTB is bone and joint

Case #3

- A 21-year-old male presented to the ED with severe neck pain without history of trauma
- Symptoms progressed over six months
- He denied fever, chills, cough, difficulty swallowing, leg/arm weakness, bowel/bladder incontinence, change in appetite, or other sites of pain
- Born in Guatemala, he had been in the U.S. for two years working as a dishwasher
- He denied both exposure to Tuberculosis (TB) and history of any TB screening
Case #3 - Clinical Course

- US guided biopsy of neck mass - AFB smear negative
- Bronchoscopy - no endobronchial lesions, washings AFB smear negative
- TST 14 mm
**Case #3 - Clinical Course**

- Initiated IRZE
- Surgery considered
- Aggressive Pain Control -
  - 100 micrograms of Duragesic patches every 72 hours coupled with 600 mg ibuprofen with each meal and PRN Percocet.
- Close follow-up

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**Case #3 - Clinical Course**

- Organism was recovered at culture 2 weeks later (aspirate, sputa and FOB)- fully susceptible
- One year treatment
- Tapered off pain medications by 6 months of treatment
- At end of therapy, normal radiographic appearance of his cervical spine
- Able to avoid surgery and lifelong hardware in this young man
Vertebral TB (TB Spondylitis)

Origin of vertebral osteomyelitis in anterior inferior edge of vertebra adjacent to disc

Abscess filled with necrotic debris
(“cold” as opposed to “hot” abscess filled with pyogenic pus)
Pathophysiology and Treatment

- Caused by hematogenous spread and seeding during initial infection
- Treatment length- Guidelines state that EPTB should be treated similar to pulmonary except in cases slow to respond where treatment may be lengthened
  - 12 months (my preference)

Clinical Pearls

- Indications for surgery include neurologic compromise or inability to control pain
  - The radiologic findings though frightening should not drive the decision
- Pain management must be aggressive and the interactions with Rifampin must be taken into account
  - Rifampin increased P450 system in liver causing increased metabolism of narcotics
Clinical Pearls

- Ideally, diagnosis of spinal TB is made by a combination of imaging, preferably MRI, and culture of *Mycobacterium tuberculosis* from biopsy samples.
- Often the spinal lesions are accompanied by the presence of a large paraspinal abscess or fluid collections. The presence of such abscesses, often referred to as “cold abscesses,” in the absence of fever, is very suggestive of TB.

CNS TB

4.5% of EPTB
CNS TB: Meningitis Commonest Form

TB Meningitis

- Prodrome
  - 2-3 weeks
  - Malaise, fever, anorexia, behavioral changes
- Wide initial clinical spectrum
  - Vomiting
  - Increased drowsiness
  - Focal neurologic signs
  - Meningismus
- Stupor, coma, and death over 5-8 weeks\(^1\)
- Complications – hydrocephalus, infarcts due to vasculitis, tuberculoma/abscess

TB Meningitis - Diagnosis

- CSF
  - Opening pressure
  - Protein, glucose
  - Cell differential
  - AFB smear and culture
  - Xpert
    - Sensitivity 63% Specificity 98%
    - Sensitivity is increased to 84% with concentration (centrifugation)
  - TST
    - Negative in > 50% cases

TB Meningitis: Hydrocephalus complication
Ventriculostomy or Ventriculo-peritoneal shunt
TB Meningitis – Treatment

- Timing is critical: 90% of deaths occur early\(^1\)
- Drugs: meningeal penetration
  - Good: INH, PZA, SM; less good RIF, EMB
  - Parenteral forms
  - Debate in children: EMB vs ETH
  - Studying high dose rifampin/IV and fluoroquinolone
  - Generally use same regimens as PTB
- 12 months, daily

\(^1\)Schaaf & Zumla, eds. Tuberculosis. 2009

TB Meningitis

- Repeat lumbar puncture, especially early on to follow disease
- Neurosurgical referral for hydrocephalus, CNS abscesses and paraplegia
Recommendation for Corticosteroid Use

- Use based on outcome by clinical stages
- Original standard by BMRC: use in Stage II-III
- Iseman: all stages; adjust dose for RIF effect\(^1\)
- Vietnam trial: lower mortality all stages\(^2\)
- Current guidelines – use corticosteroids and taper over 6-8 weeks

\(^1\)M. Iseman. *A Clinician’s Guide to Tuberculosis*. 2000
\(^2\)G. Thwaites, Nguyen & Nguyen. *NEJM*. 2004
\(^3\)P. Singh, *Cochrane Database of Systematic Reviews 2008*, Issue 1, Art 1
Nahid, Tuberculosis treatment, 2016

Pericardial TB: “Water-Bottle” Silhouette
Pericardial TB

- Indirect diagnosis (TB elsewhere), pericardial tap, or clinical diagnosis
- Treat promptly: potentially lethal tamponade
- RIPE
- Corticosteroids no longer routinely recommended, based on more recent studies
- Monitor to rule out constriction
- May require pericardiectomy

Prednisolone and Immunotherapy in TB Pericarditis

- 1400 patients with definite or probable Pericardial TB; 2/3 concomitant HIV infection
- Prednisolone vs Placebo as well as M.Indicus pranii vs placebo
- Primary Outcomes: Death, Cardiac Tamponade or Constrictive pericarditis
- No differences seen

Prednisolone and Mycobacterium indicus pranii in Tuberculous Pericarditis
Mayosi et al.
Female Genital (pelvic) TB

- Lympho-hematogenous, rarely sexual transmission
- Tubes, endometrium, ovaries
- Presentation:
  - Pelvic pain
  - Menometorrhagia; vaginal discharge
  - Infertility (common in developing world)
E-P TB Diagnostic Pitfall: “Think TB”

- Thank TB when the workup does not reveal usual suspects
- Historical clues often overlooked and are key
  - Origin/travel from TB endemic country
  - Past TB exposure; FH of TB
  - Prior (+) TST or (+) IGRA
  - Past TB disease, treated or untreated
  - Radiologic evidence for prior, healed TB
- Think TB in persons who have:
  - Risk factors for TB infection
  - Risk factors for progression to TB disease

E-P TB Treatment

<table>
<thead>
<tr>
<th>Site</th>
<th>Length of therapy (mo)</th>
<th>Rating (duration)</th>
<th>Corticosteroids[1]</th>
<th>Rating (corticosteroids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node</td>
<td>6</td>
<td>Al</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>6–9</td>
<td>Al</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Pleural disease</td>
<td>6</td>
<td>Al</td>
<td>Not recommended</td>
<td>DII</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>6</td>
<td>Al</td>
<td>Strongly recommended</td>
<td>Al</td>
</tr>
<tr>
<td>CNS tuberculosis including meningitis</td>
<td>9–12</td>
<td>BIII</td>
<td>Strongly recommended</td>
<td>AI</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>6</td>
<td>Al</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6</td>
<td>Al</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Pleural</td>
<td>6</td>
<td>Al</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
</tbody>
</table>

\[1\] Rating system, see Table 1.
\[2\] Duration of therapy for extrapulmonary tuberculosis caused by drug-resistant organisms is not known.
\[3\] Corticosteroid preparations vary among studies. See Section II.3 for specific recommendations.

ATS/IDSA/CDC 2003
Use of Xpert in EP TB

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node</td>
<td>83%</td>
<td>81%</td>
<td>Culture/CRS</td>
</tr>
<tr>
<td>CSF</td>
<td>80.5%</td>
<td>62%</td>
<td>Culture/CRS</td>
</tr>
<tr>
<td>Pleural Fluid</td>
<td>46%</td>
<td>21%</td>
<td>Culture/CRS</td>
</tr>
</tbody>
</table>

Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis
C Denkinger et al.

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