Extrapulmonary Tuberculosis
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Disclosure / Disclaimer

• No financial conflicts of interest

• No mention of off-label use of FDA-approved medications
Objectives

Extrapulmonary Tuberculosis

• Identify how the traditional patterns of extra pulmonary vs pulmonary TB are changing

• Review the challenges in diagnosis with extra pulmonary disease

• Review the challenges in case management with extra pulmonary disease
Extrapulmonary Tuberculosis

• The overall decline in TB cases since 1953 has been almost exclusively due to a reduction in pulmonary TB, with extra-pulmonary TB remaining relatively constant.

• Explanations that have been proposed include:
  - The increased burden of chronic diseases*
  - Immigration patterns*
  - The increase in the use of immune suppressant medications*

TB Cases by Site of Disease USA – 2015**

Number of cases

- 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.
Table 38. Tuberculosis Cases and Percentages, by Pulmonary and Extrapulmonary Disease: Reporting Areas, 2015

<table>
<thead>
<tr>
<th>Reporting area</th>
<th>Total cases</th>
<th>Pulmonary(^1)</th>
<th>Extrapulmonary(^2)</th>
<th>Both pulmonary/ extrapulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>9,557</td>
<td>6,668 (69.8)</td>
<td>1,933 (20.2)</td>
<td>950 (9.9)</td>
</tr>
<tr>
<td>Illinois</td>
<td>343</td>
<td>235 (68.5)</td>
<td>81 (23.6)</td>
<td>27 (7.9)</td>
</tr>
<tr>
<td>Indiana</td>
<td>116</td>
<td>75 (64.7)</td>
<td>28 (24.1)</td>
<td>13 (11.2)</td>
</tr>
<tr>
<td>Iowa</td>
<td>38</td>
<td>26 (68.4)</td>
<td>9 (23.7)</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Michigan</td>
<td>131</td>
<td>74 (56.5)</td>
<td>44 (33.6)</td>
<td>13 (9.9)</td>
</tr>
<tr>
<td>Minnesota</td>
<td>150</td>
<td>79 (52.7)</td>
<td>53 (35.3)</td>
<td>18 (12.0)</td>
</tr>
<tr>
<td>Ohio</td>
<td>143</td>
<td>98 (68.5)</td>
<td>45 (31.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
### Extrapulmonary (E-P) TB in USA – 2015**

<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>

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

*Excludes those with both pulm/extrapulmonary

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

Table 39. Extrapulmonary Tuberculosis Cases and Percentages by Site of Disease: Reporting Areas, 2015

<table>
<thead>
<tr>
<th>Reporting area</th>
<th>Total extrapulm. cases</th>
<th>Total extrapulm. sige*</th>
<th>Pleural</th>
<th>Lymphatic</th>
<th>Bone or joint</th>
<th>Genitourinary</th>
<th>Meningeal</th>
<th>Peritoneal</th>
<th>Laryngeal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1,933</td>
<td>2,032</td>
<td>349</td>
<td>715</td>
<td>196</td>
<td>91</td>
<td>92</td>
<td>126</td>
<td>4</td>
<td>459</td>
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<tr>
<td>Illinois</td>
<td>81</td>
<td>86</td>
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<td>34</td>
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<td>28</td>
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<td>4</td>
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<tr>
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<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Michigan</td>
<td>44</td>
<td>44</td>
<td>9</td>
<td>12</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Minnesota</td>
<td>53</td>
<td>55</td>
<td>2</td>
<td>33</td>
<td>11</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Ohio</td>
<td>45</td>
<td>45</td>
<td>6</td>
<td>15</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>
Extrapulmonary TB

• Overall rates of TB declining, proportion of EPTB increasing
• Associated with women, foreign-birth, nonwhite race, immune-compromise
• Not associated with MDR, incarceration, alcoholism, homelessness (US)

Peto, CID, 2009
Fiske, BMC ID, 2010
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
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$^1$

$^1$H.Schaaf & A.Zumla, eds. *Tuberculosis*. 2009
Demographics of E-P Disease

- Highest rates in productive years\(^1\)
- Nodal TB highest in females and young ages\(^1\)
- TB of bones and joints trending up\(^1\)
- Immunosuppression influences miliary rates\(^2\)
- Racial/ethnic disparities meningeal/pericardial\(^3\)

\(^1\)Prakasha, SR et al. J.Glob.Inf Dis. 2013,52.
\(^3\)Iseman, M. A Clinician’s Guide to Tuberculosis. 2000.
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)
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 Stages

• Stage I: fully conscious, rational, and do not have neurologic signs
• Stage II: confused or have neurologic signs such as cranial nerve palsy or hemiparesis
• Stage III: coma or stupor with more severe neurologic signs
TB Meningitis – Diagnosis

• CSF exam
  ▪ Opening pressure; protein; glucose
  ▪ Cell differential
  ▪ AFB smear, NAA, culture

• TST (−) in > 50%
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

• Vietnam trial: lower mortality all stages

• Current guidelines – use corticosteroids and taper over 6-8 weeks

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2G.Thwaites, Nguyen & Nguyen. NEJM. 2004
3P.Singh. Cochrane Database of Systematic Reviews 2008, Issue 1, Art 1 Nahid, Tuberculosis treatment, 2016
CNS Tuberculoma
CNS Tuberculomas

- Can occur w steroid taper in TB meningitis
- Biopsy if no other site diagnostic
- Serial MRIs/CTs to follow
- Up steroid dose if paradoxical response
- Treat 12 months or until edema resolved

1 S. Poonoose et al. *Neurosurgery*, 2003
Pericardial TB

• From hematogenous or lymph node spread

• Dyspnea, cough, chest pain, ankle swelling, night sweats

• Pleural effusion frequently associated

• Low voltage EKG

• CXR: cardiomegaly; confirm on ECHO or CT
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\(^1\)
- Monitor to rule out constriction
- May require pericardiectomy

Bone & Joint TB

- Common crippling disease in 1900
- 3rd most common E-P site
  - ~ 3-4% of TB cases, 10-11% of E-P
  - Higher in HIV (+)
- Pain, impaired function, swelling; slow course
- Pulmonary disease in 30-50%
- 9 months treatment, 12 m if hardware (opinion)
Case Example

• 29 year old software engineer originally from India, with bilateral leg pain for 4 years but recently worse on the right

• He noted ankle swelling about 1 year ago, but only recently saw his physician for this complaint

• He denied any other symptoms
September 2011
What is your next step in management?

A. This is likely a sports injury, reassure him and refer him to physical therapy

B. Start IV antibiotics immediately for this foot abscess

C. Recommend biopsy of the affected area

D. Refer to Oncology for treatment of bone tumor
January 2012

• Underwent partial excision of fibula + deep biopsy of soft tissue and bone
• Operative findings: soft tissue mass and lateral malleolus erosion
• Frozen and final path: necrotizing granulomas
Microbiology

• Tissue and bone specimens: AFB smear neg
• Re-review of path specimen: solitary AFB
• MTB PCR + on tissue
• Tissue and bone specimens: MTB culture +
What would you do next?

A. Start standard 1\textsuperscript{st} line therapy for tuberculosis disease

B. Wait for drug susceptibility testing

C. Recommend further surgical debridement

D. This is likely a false positive, recommend another biopsy
Prior History

- Cough, fever, weight loss while in Denmark
- Treated for pneumonia
- TST+
- Persistent symptoms
- Treated for TB x 6 months
- Symptoms resolved

- Moved to US
- Developed ankle swelling

2006  2007  2011
<table>
<thead>
<tr>
<th>Anatomical site</th>
<th>Patients (n)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>29</td>
<td>47.6</td>
</tr>
<tr>
<td> Cervical</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td> Thoracic</td>
<td>8</td>
<td>13.2</td>
</tr>
<tr>
<td> Thoracic/lumbar</td>
<td>4</td>
<td>6.6</td>
</tr>
<tr>
<td> Lumbar</td>
<td>10</td>
<td>16.4</td>
</tr>
<tr>
<td> Not classified</td>
<td>5</td>
<td>8.2</td>
</tr>
<tr>
<td>Humerus/elbow</td>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>Knee</td>
<td>5</td>
<td>8.2</td>
</tr>
<tr>
<td>Chest wall</td>
<td>5</td>
<td>8.2</td>
</tr>
<tr>
<td>Hip/femur</td>
<td>4</td>
<td>6.6</td>
</tr>
<tr>
<td>Pelvis/SIJ</td>
<td>4</td>
<td>6.6</td>
</tr>
<tr>
<td>Wrist</td>
<td>3</td>
<td>4.9</td>
</tr>
<tr>
<td>Fingers</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Ankle</td>
<td>1</td>
<td>1.6</td>
</tr>
</tbody>
</table>


Mayo Clinic Center for Tuberculosis
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)
Vertebral TB, Paraspinal Abscess
Vertebral TB – Surgical Indications

• Generally, surgical debridement doesn’t add to medical therapy; medical therapy alone often enough

• Relieve neurological symptoms; prevent progression
  - Neurologic deficit, cord compression
  - Instability or pain
  - >50% destruction of vertebra
  - Large abscesses
  - Non-diagnostic needle biopsy
  - Poor response to medical therapy
TB Lymphadenitis & Fashion Trend

At left, reproduced by permission of Lady Alexandra Cavendish-Bentinck ©1974 Ruth Lloyd Miller

A portrait of Edward de Vere, 17th Earl of Oxford, who some think wrote Shakespeare’s plays, left; an engraving of Shakespeare, right.
TB Lymphadenitis

- Most frequent E-P site

- Foreign-born with TB, HIV (+) higher

- Within 6 mo of primary infection: most regress\(^1\)

- Excisional biopsy reduces fistulas, but generally not needed and avoided

- Sputum cultures even with (-) CXR

- Treatment generally 6 months

\(^1\)E. Lincoln & E. Sewell. *Tuberculosis in Children*. 1963
Peritoneal TB

• Most at-risk
  ▪ Young child-bearing age women
  ▪ Older men, often alcoholic

• Presentation
  ▪ Ascites
  ▪ Abdominal pain, with or without obstruction

• False (+) CA125; resolves on treatment
  ▪ Marker for epithelial ovarian cancer
  ▪ Some benign conditions
Case
82 y.o. woman from Peru on TNF blocker for RA with 1 month of early satiety, weight loss and abdominal bloating. Abdominal ultrasound with +ascites. CA-125 elevated.
Case

- Biopsy of omentum revealed granulomatous inflammation
- Lung biopsy grew MTB
- With treatment CA-125 improved (897 to 41)
Pleural TB

• Acute > subacute chest pain
• Fever, shortness of breath, cough
• Usually unilateral, moderate sized
• Pulmonary lesion seen better on CT scan
• Exudative, lymphocytic effusion by laboratory analysis
• Adenosine deaminase (ADA) useful in diagnosis
Pleural TB

- Diagnose on pleural tissue and pleural fluid
- High yield sputum culture even without infiltrate
- Steroids likely not beneficial
- Resolution without treatment usual
- Pulmonary TB occurs later if no Rx
Genitourinary TB

• Renal TB hematogenous origin
  ▪ Urinary abnormalities: RBCs, WBCs

• Male genital TB via urine/contiguous spread to bladder, epididymis, testes, and/or prostate. 50% become sterile
  ▪ Local presentation; rarely systemic symptoms; superinfection frequent (may be treated with quinolone, suppressing TB!)
  ▪ Ureteral obstruction may require stent or nephrostomy
Genitourinary TB

- Urinalysis positive without + routine bacterial culture
  - Sterile Pyuria
- Urine culture + MTB
- Positive urine culture sometimes seen in advanced HIV and is more reflective of disseminated TB
Female Genital (pelvic) TB

- Lympho-hematogenous, rarely sexual transmission
- Tubes, endometrium, ovaries

- Presentation:
  - Pelvic pain
  - Menometrorrhagia; vaginal discharge
  - Infertility (common in developing world)
Disseminated TB

- Medical risk factors
  - Immunosuppression, HIV/AIDS, age extremes
  - Cancer, cancer chemotherapy
  - TNF inhibitor agent, corticosteroids

- In USA, shift from pediatric age group to adults
- More than one noncontiguous sites
- “Miliary” if lesions 1-2 mm
Extrapulmonary TB Diagnosis

- Tends to be paucibacillary, and more difficult to detect microbiologically
- May require invasive + repeated procedures
- Rapid Tests may be helpful
  - Nucleic Acid Amplification Tests
  - GeneXpert MTB/RIF

Laraque, CID, 2009
Hillemann JCM, 2011
Tortoli, ERJ, 2012
E-P TB Diagnostic Pitfall: “Think TB”

• Historical clues often overlooked
  ▪ 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
Clinical Pearls:

- Abnormal E-P system in setting of active pulmonary TB
- If monoarticular arthritis; vertebral lesion; or infertility
- “Sterile” pyuria
- Lymphocytic csf/pleural/peritoneal/joint fluid
- Very high ESR, C-reactive protein
- Possible false (+) CA-125
- Typical histopathology on biopsy or surgical specimens
# Extrapulmonary TB Treatment

<table>
<thead>
<tr>
<th>Site of disease</th>
<th>Length of Therapy (months)*</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node</td>
<td>6</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>6-9</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Pleural disease</td>
<td>6</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>6</td>
<td>Not recommended</td>
</tr>
<tr>
<td>CNS tuberculosis including meningitis</td>
<td>9-12</td>
<td>Strongly recommended</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>6</td>
<td>Not recommended</td>
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<tr>
<td>Genitourinary</td>
<td>6</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>6</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

- TB regimen based on drug susceptibility – if available
- Duration of treatment based on clinical and radiological improvement
Challenges in E-P TB

- Fewer TB cases has likely led to ↓ suspicion for TB
- Public health focus is primarily on PTB
- Differing risk factors
- Diagnosis often more difficult and delayed
- Treatment efficacy + culture conversion can be difficult to detect
Approach to E-P TB

• Utilize a multidisciplinary approach involving surgery, pathology, radiology, TB expert, public health

• Parallel care for complications (e.g. Ortho in Pott’s; Neuro/Neurosurgeon for CNS)

• May need serial procedures or imaging to follow

• Consult experts (TB, laboratorians, and otherwise)

• Engage public health sector

• Teach providers in your communities to recognize E-P TB (early)
Work-up

- Identify risk factors
- TST/IGRA
- CXR
- (sputum AFB smear/CX)
- Site specific Diagnosis
- AFB smear, Culture, Mtb PCR
- Radiology
- Started on 4 drug anti-TB therapy
- Drug susceptibility
Mahalo! Thank you! “Kap kun kah”
Acknowledgements

• Amee Patrawalla, MD
  Global Tuberculosis Institute, Newark, New Jersey
• Pamela B. Hackert, MD, JD, MPH
  Oakland County Health Division, Michigan