Extrapulmonary Tuberculosis
XPTB

Shannon Kasperbauer, MD
National Jewish Health
Denver TB Course
April 2017
The Kings Evil

“...strangely visited people all swol’n and ulcerous, pitiful to the eye, the mere despair of surgery, he cures, hanging a golden stamp about their necks, put on with holy prayers; and ‘tis spoken, to the succeeding royalty he leaves the healing benediction...”

Shakespeare, Macbeth
• Autopsy on adult inpatients: 4/12-5/13
• N: 125
• 64% male, 81% HIV +
  78 (62%) had TB
  20/78 (26%) undiagnosed TB
  13/78 (13%) undiagnosed MDR TB
  35/78 (45%) XPTB
XPTB higher in HIV patients (OR 5.14)

Incidence of Extrapulmonary Tuberculosis

Figure 1. Pulmonary and extrapulmonary tuberculosis cases, United States, 1964-1976. (*Criteria for counting reported cases changed in 1975.*)
XPTB: 2015 US Cases (n= 1933)

Leading cities
1. CA  21.5%
2. TX 10.9%
3. NY  7.8%

www.cdc.gov/tb/statistics
Risk factors for XPTB

- Untreated Human immunodeficiency virus (HIV) infection*
- Corticosteroids or other iatrogenic immunosuppression
  - (i.e, TNF-α blocking agents)*
- Infancy*
- Female sex (OR 1.7)
- Alcohol abuse
- Malignancy
- Connective tissue disease
  - (with or without iatrogenic immunosuppression)
- Renal failure
- Diabetes
- Pregnancy
- Vitamin D deficiency*

Question

- 23 year old male with HIV/AIDS presents with unilateral **painless** cervical lymphadenopathy:
  
  A. Obtain a biopsy for afb smear/culture as well as routine and fungal cultures.
  
  B. This is an unusual presentation for TB therefore a biopsy for pathology is warranted.
  
  C. Begin empiric TB therapy as this is most likely TB.
Challenges in the diagnosis of XPTB

• Signs and symptoms are nonspecific
• Appropriate specimens must be obtained for microscopy/culture and histology
• Serial cultures may not be readily available/feasible on treatment
Diagnosis

Syringe on catheter removing fluid from around the lung

Vacuum bottle collecting pleural fluid

Swollen lymph node

Normal lymph node

Spinal needle is inserted between 3rd and 4th lumbar vertebrae.

Cerebrospinal fluid
XPTB in New Delhi
Six years experience in a reference lab

![Bar chart showing total cases of XPTB types: Total, INH-R, MDR, XDR]

**Total cases**

<table>
<thead>
<tr>
<th>Type</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>200</td>
</tr>
<tr>
<td>INH-R</td>
<td>150</td>
</tr>
<tr>
<td>MDR</td>
<td>50</td>
</tr>
<tr>
<td>XDR</td>
<td>0</td>
</tr>
</tbody>
</table>

**KEY POINT**

- In some areas of the world, resistance is seen in over 30% of cases, therefore CULTURE AND DRUG SUSCEPTIBILITY are of critical importance

XPTB + HIV

- XPTB more common in HIV/AIDS
- Increasing rate with decreasing CD4
- #1 Lymphadenitis
- #2 Disseminated
  - Similar to GNR bacteremia, sepsis, death
- Obtain directed bx, sputum, blood, urine afb cultures
Lymphatic Tuberculosis

- Spread from local infection
- Painless
- Unilateral
- Cervical chain most common
- Biopsy
- Chemotherapy (6 mo)
- Be prepared for paradoxical reactions
  - (up to 23%)
Pleural Tuberculosis

- Delayed hypersensitivity vs. TB infection
- Unilateral, sm-moderate sized
- Parenchymal disease 50%
- Fever, np cough, pleurisy
- Thoracentesis (Cx + < 30%)
- Exudate, high protein, high LDH, low pH, low glucose
- Lymphocytic pleocytosis
- Pleural biopsy Cx + ~ 90%
- Chemotherapy (6 mo)
## Diagnosis of Pleural TB

<table>
<thead>
<tr>
<th></th>
<th>AFB smear (%)</th>
<th>AFB culture (%)</th>
<th>Histology (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fluid</td>
<td>0-10</td>
<td>23-58</td>
<td></td>
</tr>
<tr>
<td>Pleural tissue</td>
<td>14-39</td>
<td>40-85</td>
<td>69-97</td>
</tr>
</tbody>
</table>

Lewinsohn CID 2017

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Gene Xpert</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural TB</td>
<td>46</td>
<td>21</td>
</tr>
</tbody>
</table>

Denkinger Eur Resp J 2014

### Meta-analysis in pleural TB (n= 1626)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>INF-γ</td>
<td>89</td>
<td>97</td>
</tr>
</tbody>
</table>

Zhou Scientific reports 2015
Genitourinary Tuberculosis

- Pain, altered urination
- Sterile pyuria, hematuria, proteinuria
- Imaging: hydronephrosis, distortion of the collecting system
- Urine: Smear not performed
- Urine Culture AFB + (80-94%)
- Chemotherapy (6mo)
• What is this woman doing?
A. Brushing her teeth
B. Shining light into her throat
C. Performing a self exam
Laryngeal Tuberculosis

- Hoarseness, odynophagia
- True vocal cords
- Unilateral
- Variable pathology
- Historically a complication of pulmonary TB
- Prognosis usually good, immobility can be reversible
- Chemotherapy (6mo)
- Surgery reserved for airway compromise

http://www.sciencedirect.com/science/journal/01945998
Gastrointestinal Tuberculosis

- Hepatic, enteritis, peritonitis
- Abdominal pain, fever, ascites
- 70% have sx for > 4 months
- Ascites: lymphocytic exudate
  - beware of dilution in cirrhosis
- Ascites:
  - Smear usually negative.
  - Culture + 45-69%
- Peritoneal biopsy
- Chemotherapy (6mo)

Lewinsohn CID 2017
A 48 year old male from South Africa complains of chest pain that worsens with leaning forward. ECG notes PR depression and diffuse ST elevation.

A. Begin Rifampin/INH/PZA/EMB as TB pericarditis is the most likely diagnosis.

B. Begin Rifampin/NH/PZA/EMB and steroids after a pericardial biopsy for afb smear/culture and TB PCR.

C. Request a pericardiocentesis for afb smear and culture. A negative result excludes the diagnosis.
Pericardial Tuberculosis

- Rupture of a mediastinal lymph node
- Cough, wt loss, dyspnea, orthopnea, chest pain, edema, fever
- Tachycardia, cardiomegaly, JVD, muffled sounds, 1/2 with friction rub
- ECG: ST/TW depression, CXR enlarged heart, echo: effusion, constrictive pericarditis
- Pericardial biopsy:
  - send for smear/culture and PCR
- Negative biopsy does not exclude the diagnosis
- Chemotherapy (6 mo) + steroids
## Diagnosis of Pericardial TB

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>AFB smear (%)</th>
<th>AFB culture (%)</th>
<th>Histology (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial Fluid</td>
<td>0-42</td>
<td>50-65</td>
<td>73-100</td>
</tr>
</tbody>
</table>

Lewinsohn CID 2017

### Suspected Pericardial TB
(151 suspect/74 definite/50 probable)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA (&gt;35 IU/L)</td>
<td>95.7</td>
<td>84</td>
</tr>
<tr>
<td>IFN-(\gamma) (&gt;44 (\mu)g/ml)</td>
<td>95.7</td>
<td>96.3</td>
</tr>
<tr>
<td>Gene Xpert</td>
<td>63.8</td>
<td>100</td>
</tr>
</tbody>
</table>

Pandie BMC Med 2014
Adjunctive steroids in pericarditis?

- Small studies had shown a mortality benefit in patients who received corticosteroids.
- Recent RCT (n=1400) did not find a difference in the combined primary endpoint of mortality, cardiac tamponade, or constrictive pericarditis.
- In a subgroup analysis: It did suggest a benefit in preventing constrictive pericarditis.
  - large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction.

2016 Guidelines:

- Adjunctive corticosteroids should not be used routinely in the treatment of patients with pericardial tuberculosis.
- However, selective use of corticosteroids in patients who are at the highest risk for inflammatory complications might be appropriate.

Nahid CID 2016;63(7):e147–95
Spinal Tuberculosis - Pott's disease

- Lower thoracic and lumbar vertebrae
- Back pain, cold abscess, nerve root compression, *scoliosis, limp
- Bone destruction, anterior wedging, paraspinous abscess
- Biopsy for smear and culture
- Chemotherapy 6 (IIB) months +/- surgery
- Extend 9-12 months for advanced disease
Extra-spinal bone/joint tuberculosis

- Osteomyelitis < arthritis
- hip and knee
- Cold abscess, pain, swelling, loss of joint function
- Constitutional symptoms <30%
- X-ray findings may be nonspecific, destruction is a late finding
- Bone/synovial biopsy for smear and culture
- Chemotherapy for 6 months
- 9-12 months for advanced disease
Osteomyelitis of the wrist and forearm
Shoulder septic arthritis
Distal clavicular osteolysis
Outbreak of XPTB associated with acupuncture, China

- 33 XPTB cases
  - all confirmed MTB, Beijing strain
Case Question

• 9 month old with subacute altered mental status, facial droop
• Evidence of lymphocytic pleocytosis on CSF, low glucose and high protein

• While waiting for the diagnostic studies:
  1. Begin ceftriaxone and vancomycin
  2. Begin dexamethasone, ceftriaxone and vancomycin
  3. Begin dexamethasone, ceftriaxone, vancomycin, INH, RIF, ETH, PZA
CNS Tuberculosis

- Hematogenous or direct
- 3 Stages
- OP on LP normal or high
- CSF analysis:
  - Lymphocytic pleocytosis
  - elevated protein
  - low glucose
  - Send off the 4th tube
  - minimum of three serial lumbar punctures should be performed at daily intervals

DO NOT DELAY TREATMENT FOR + DIAGNOSTICS
Phases of TB meningitis

<table>
<thead>
<tr>
<th>Phase</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodromal phase (2-3 weeks)</td>
<td>Malaise, headache, low grade fever, personality change</td>
</tr>
<tr>
<td>Meningitic phase</td>
<td>Neurologic features: meningismus, protracted headache, emesis, lethargy, confusion, CN signs</td>
</tr>
<tr>
<td>Paralytic phase</td>
<td>Confusion, stupor, coma, seizures, hemiparesis and death</td>
</tr>
</tbody>
</table>
CNS Tuberculosis

- Look elsewhere for dissemination
- 1/3 have miliary TB
  - check eyes
- Smear/culture
- PCR of CSF
  - WHO recommends XPERT MTB/RIF

# Diagnosis of TB in the CSF

<table>
<thead>
<tr>
<th></th>
<th>AFB smear (%)</th>
<th>AFB culture (%)</th>
<th>Histology (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>10-30</td>
<td>45-70</td>
<td></td>
</tr>
</tbody>
</table>

Lewinsohn CID 2017

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Gene Xpert</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>81</td>
<td>63</td>
</tr>
</tbody>
</table>

Denkinger Eur Resp J 2014

## Suspected TB Meningitis (1490 suspect/92 diagnosed)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA (&gt;2U/L)</td>
<td>85.9</td>
<td>77</td>
</tr>
</tbody>
</table>

Ekermans BMC 2017
# Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Daily Dose (max dose)</th>
<th>Treatment Last 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Treatment Arm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH RIF PZA EMB +/- SM</td>
<td>5mg/kg (300mg)</td>
<td>INH RIF</td>
</tr>
<tr>
<td></td>
<td>10mg/kg</td>
<td>5mg/kg (300mg)</td>
</tr>
<tr>
<td></td>
<td>25 mg/kg (2gm)</td>
<td>10mg/kg</td>
</tr>
<tr>
<td></td>
<td>20mg/kg (1200mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20mg/kg (2gm)</td>
<td></td>
</tr>
<tr>
<td><strong>Intensified Treatment Arm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH RIF PZA EMB LEVO +/- SM</td>
<td>15mg/kg</td>
<td>INH RIF</td>
</tr>
<tr>
<td></td>
<td>20mg/kg</td>
<td>5mg/kg (300mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15mg/kg</td>
</tr>
</tbody>
</table>

### Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Intensified</th>
<th>Hazard Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of death/N</td>
<td>114/409</td>
<td>113/408</td>
<td>0.94 (0.73–1.22)</td>
<td>0.66</td>
</tr>
<tr>
<td>HIV infected</td>
<td>68/174</td>
<td>68/175</td>
<td>0.91 (0.65–1.27)</td>
<td>0.57</td>
</tr>
<tr>
<td>Isoniazid resistance</td>
<td>16/41</td>
<td>11/45</td>
<td>0.45 (0.20–1.02)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Summary:**
- Well designed RCT in Vietnamese Adults with TB meningitis
- No advantage associated with the use of this intensified treatment regimen, with regard to overall mortality (28%)

Summary:

- 6-month mortality in moxifloxacin arms (42% and 63%) did NOT differ significantly from that associated with the regimen without moxifloxacin (45%)
- Mortality was lower in the higher IV rifampin vs. standard oral rifampin dose of 10 mg per kilogram (34% vs. 65%)

# 2016 Guidelines
## Treatment of TB meningitis

1. INH, RIF, PZA, and EMB in an initial 2-month phase.
2. After 2 months of 4-drug therapy, for meningitis known or presumed to be caused by susceptible strains, PZA and EMB may be discontinued, and INH and RIF continued for an additional 7–10 months.
3. Adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks
4. Repeated lumbar punctures early in the disease should be considered to document response to therapy.

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Nahid CID 2016;63(7):e147–95
### Short Intensified Treatment in Children with Drug-susceptible Tuberculous Meningitis

- **184 Children**
- **80% having stage 2-3 (BRMC classification)**
- **6 months /4 drug treatment**
  - isoniazid (15 to 20 mg/kg)
  - rifampin (20 mg/kg)
  - pyrazinamide (40 mg/kg)
  - ethionamide (20 mg/kg)
- **Overall mortality 3.8%**

#### Outcome after end of treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>79</td>
<td>42.9%</td>
</tr>
<tr>
<td>Mild sequelae</td>
<td>68</td>
<td>36.9%</td>
</tr>
<tr>
<td>Severe sequelae</td>
<td>30</td>
<td>16.3%</td>
</tr>
<tr>
<td>Death</td>
<td>7</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

#### Relapse rate of treatment survivors

- Home-based treatment (n = 90)
  - No relapses (cured) 88
  - Death 2
  - Lost to follow up 0

- In-hospital treatment (n = 87)
  - No relapses (cured) 52
  - Death 6
  - Lost to follow up 29

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*Data adapted from Pediatr Infect Dis J 2014;33:248–252*
TB meningitis in Children

American Academy of Pediatrics recommends an initial 4-drug regimen of INH, RIF, PZA, and an aminoglycoside or ethionamide for 2 months, followed by 7–10 months of INH and RIF
Dexamethasone in CNS TB

Dexamethasone was associated with a reduced risk of death (relative risk, 0.69; 95 percent confidence interval, 0.52 to 0.92; P=0.01)

2016 TB Treatment Guidelines: recommend adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks with tuberculous meningitis

Table 3. Outcomes of 545 Patients Nine Months after Randomization.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Outcome number (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Good</td>
</tr>
<tr>
<td>Dexamethasone*</td>
<td>274</td>
<td>104 (38.0)</td>
</tr>
<tr>
<td>Placebo</td>
<td>271</td>
<td>95 (35.1)</td>
</tr>
</tbody>
</table>

Cochrane Database Syst Rev. 2008
Early Clues in disseminated TB
Miliary TB in a newborn

http://www.mevis-research.de
Disseminated Tuberculosis

- Primary or secondary hematogenous infection
- Insidious, cryptic fever, weight loss
- Rare: ARDS, DIC, pancytopenia
- CXR often atypical or normal
- PPD and sputum negative in up to 50%
- Investigate involved organs
- Chemotherapy 6+ months
## XPERT MTB RIF in XPTB diagnosis
### Meta-analysis

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fluid</td>
<td>0.34 (95% CI, 0.24–0.44)</td>
<td>0.98 (0.96 – 0.99)</td>
</tr>
<tr>
<td>Non pleural serous fluid</td>
<td>0.67 (IQR, 0.00-1.00)</td>
<td>1.00 (1.00 – 1.00)</td>
</tr>
<tr>
<td>Gastric aspirate</td>
<td>0.78 (IQR, 0.68 – 0.85)</td>
<td>1.00 (0.99 – 1.00)</td>
</tr>
<tr>
<td>CNS fluid</td>
<td>0.85 (IQR, 0.75-1.00)</td>
<td>1.00 (0.98 – 1.00)</td>
</tr>
<tr>
<td>Lymphatic TB</td>
<td>0.96 (95% CI, 0.72-0.99)</td>
<td>1.00 (0.94 – 1.00)</td>
</tr>
<tr>
<td>Smear + specimen</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Smear – specimen</td>
<td>0.69</td>
<td></td>
</tr>
</tbody>
</table>

*BMC Infect Dis. 2014;14:709*
Diagnosing XPTB

- Culture and drug susceptibility testing remain critical in the diagnosis and should be pursued in all suspects.
- WHO: recommends Xpert as the initial test for XPTB.
- CDC/ATS/IDSA recommends NAAT testing on XPTB specimens (off-label use).
- Guidelines recommend measuring ADA and INF-γ levels in fluid when pleural, peritoneal, meningeal or pericardial TB is suspected.
- Rationale: if sensitivity is >70% and specificity is >80% then it may be beneficial.

Lewinsohn CID 2017
XPTB Treatment

• 6 Months of standard TB chemotherapy
  – Bone/Joint: consider extending treatment to 9 months
  – CNS disease 9-12 months

• The preferred frequency of dosing for extrapulmonary tuberculosis is once daily for both the intensive and continuation phases

Nahid CID 2016;63(7):e147–95
Adjunctive corticosteroids

• Steroids recommended with CNS disease (+/- pericardial disease)
  – Dexamethasone for CNS: 0.3 to 0.4 mg/kg/day for two weeks, then 0.2 mg/kg/day week three, then 0.1 mg/kg/day week four, then 4 mg per day and taper 1 mg off the daily dose each week; total duration approximately eight weeks.
  – Prednisone or prednisolone for pericardial disease (60 g/day and taper 10 mg per week; total duration of 6 weeks)