Extra-pulmonary Tuberculosis

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DENVER TB COURSE
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Disclosures

Insmed: speaker, advisory board, investigator

◦ No relevant disclosures for this talk
Objectives

- Review the epidemiology of extrapulmonary disease
- Describe host risk factors for extrapulmonary disease
- Review the presentation, diagnostic strategy and treatment of the different forms of extrapulmonary disease
- Explore the contribution of molecular techniques
- Summarize the guidelines for management
World population 7.6 Billion

TB infection 1.7 Billion

TB Disease 10 million

2017

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)

### TABLE 4.1
Notifications of TB, HIV-positive TB and MDR/RR-TB cases, globally and for WHO regions, 2017

<table>
<thead>
<tr>
<th>Region</th>
<th>Total Notified</th>
<th>New and Relapse&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PULMONARY NEW AND RELAPSE</th>
<th>Extra-Pulmonary New and Relapse (%)</th>
<th>HIV-Positive New and Relapse</th>
<th>MDR/RR-TB</th>
<th>XDR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>1 323 450</td>
<td>1 294 321</td>
<td>1 088 909</td>
<td>66%</td>
<td>16%</td>
<td>344 093</td>
<td>26 845</td>
</tr>
<tr>
<td>The Americas</td>
<td>243 064</td>
<td>228 943</td>
<td>194 228</td>
<td>78%</td>
<td>15%</td>
<td>20 487</td>
<td>4 084</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>536 185</td>
<td>523 494</td>
<td>396 945</td>
<td>53%</td>
<td>24%</td>
<td>1 327</td>
<td>4 969</td>
</tr>
<tr>
<td>Europe</td>
<td>264 563</td>
<td>220 832</td>
<td>185 826</td>
<td>64%</td>
<td>16%</td>
<td>24 722</td>
<td>48 299</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>2 965 311</td>
<td>2 826 486</td>
<td>2 403 901</td>
<td>59%</td>
<td>15%</td>
<td>61 832</td>
<td>51 788</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1 375 550</td>
<td>1 350 202</td>
<td>1 244 213</td>
<td>39%</td>
<td>8%</td>
<td>12 172</td>
<td>24 699</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td><strong>6 708 123</strong></td>
<td><strong>6 444 278</strong></td>
<td><strong>5 514 022</strong></td>
<td><strong>56%</strong></td>
<td><strong>14%</strong></td>
<td><strong>464 633</strong></td>
<td><strong>160 684</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup> New and relapse includes cases for which the treatment history is unknown. It excludes cases that have been re-registered as treatment after failure, as treatment after lost to follow up or as other previously treated (whose outcome after the most recent course of treatment is unknown or undocumented).

WHO Global TB Report

FIG. 4.6
Percentage of extrapulmonary cases among new and relapse TB cases, 2017³

Incidence of XPTB
# Incidence of XPTB

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Extra-pulmonary Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>2420</td>
</tr>
<tr>
<td>2011</td>
<td>2177</td>
</tr>
<tr>
<td>2012</td>
<td>2080</td>
</tr>
<tr>
<td>2013</td>
<td>1976</td>
</tr>
<tr>
<td>2014</td>
<td>1929</td>
</tr>
<tr>
<td>2015</td>
<td>1920</td>
</tr>
<tr>
<td>2016</td>
<td>1871</td>
</tr>
<tr>
<td>2017</td>
<td>1887</td>
</tr>
</tbody>
</table>

XPTB: 2017 n=1887

Leading cities in 2017
1. CA  n=386
2. TX  n=201
3. NY  n=171

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

• Untreated Human immunodeficiency virus (HIV) infection
• Infancy
• Corticosteroids or other iatrogenic immunosuppression
• Female sex (OR 1.7)
• Alcohol abuse
• Malignancy
• Connective tissue disease (with or without iatrogenic immunosuppression)
• Renal failure
• Diabetes
• Pregnancy
• Vitamin D deficiency

Diagnostic challenges

- SIGNS AND SYMPTOMS ARE NONSPECIFIC
- DIAGNOSTIC SAMPLING MAY BE DIFFICULT
- SERIAL SAMPLING ON TREATMENT MAY NOT BE FEASIBLE
Diagnosis
XPTB in New Delhi
High rates of drug resistance

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 AIDS
- INCREASING RATE WITH DECREASING CD4
- #1 LYMPHADENITIS
  #2 DISSEMINATED

OBTAIN AS MANY CULTURES FROM AS MANY SITES AS POSSIBLE
USE MOLECULAR TOOLS
URINE LAM

Gupta-Wright Lancet 2018
Lymphatic Tuberculosis

**PRESENTATION**
Painless, unilateral, cervical chain most common

**DIAGNOSIS**
Biopsy

**TREATMENT**
Chemotherapy (6 mo)
Be prepared for paradoxical reactions (up to 25%)
Pleural Tuberculosis

**PRESENTATION**
- Fever, cough, pleurisy
- Unilateral sm-mod effusion
- Parenchymal disease 50%

**DIAGNOSIS**
- Thoracentesis (<30%)
- Pleural Biopsy (90%)

**TREATMENT**
- Chemotherapy
  - 6 months
**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

<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

PRESENTATION
Pain, altered urination
Sterile pyuria, hematuria, proteinuria
Hydronephrosis, distortion of collecting system

DIAGNOSIS
Urine smear is not performed
Urine AFB culture, early collection

TREATMENT
Chemotherapy
6 months
What is this woman doing?

A. Brushing her teeth
B. Shining light into her throat
C. Performing a self exam
What is this woman doing?

A. Brushing her teeth
B. Shining light into her throat
C. Performing a self exam
Laryngeal Tuberculosis

**PRESENTATION**
- Hoarseness, odynophagia
- Unilateral, true vocal cords

**DIAGNOSIS**
- Laryngeal biopsy

**TREATMENT**
- Chemotherapy 6 months
- Surgery reserved for airway compromise
- Prognosis usually good, immobility can be reversible

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

PRESENTATION
Hepatitis, enteritis, peritonitis
Abdominal pain, fever, ascites
70% symptoms > 4 months

DIAGNOSIS
Ascites: lymphocytic exudate
beware of dilution in cirrhosis
Ascites: Smear usually negative.
Culture + 45-69%
Peritoneal biopsy

TREATMENT
Chemotherapy
6 months
Audience Response Question

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

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

C. Obtain a pericardiocentesis for afb smear and culture. A negative result excludes the diagnosis.
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.

Begin Rifampin/INH/PZA/EMB

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

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

PRESENTATION
Cough, wt loss, 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

DIAGNOSIS
Pericardial biopsy: Smear, culture, PCR
Negative biopsy does not exclude the diagnosis

TREATMENT
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>Test</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-γ (&gt;44 μg/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
Guidelines support selective use of steroids in pericarditis

Recent RCT (n=1400) NO difference in the combined primary endpoint of mortality, cardiac tamponade, or constrictive pericarditis

Subgroup analysis: Suggested 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
CXR
Spinal Tuberculosis- Pott’s disease

PRESENTATION
Lower thoracic and lumbar vertebrae
Back pain, cold abscess, nerve root compression *scoliosis, limp
Bone destruction, anterior wedging, paraspinous abscess

DIAGNOSIS
Biopsy for smear and culture

TREATMENT
Chemotherapy 6 months +/- surgery
Extend 9-12 months for advanced disease
Osteomyelitis of the wrist and forearm
Shoulder septic arthritis
Clavicular osteomyelitis
Extra-spinal bone/joint tuberculosis

**PRESENTATION**
- Osteomyelitis < arthritis: hip and knee
- Cold abscess, pain, swelling, loss of joint function
- Constitutional symptoms <30%

**DIAGNOSIS**
- X-ray findings may be nonspecific, destruction is a late finding
- Bone/synovial biopsy for smear and culture

**TREATMENT**
- Chemotherapy for 6 months
- 9-12 months for advanced disease
Outbreak of XPTB associated with acupuncture, China

33 XPTB cases
- all confirmed MTB, Beijing strain
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
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:

A. Begin ceftriaxone and vancomycin

B. Begin dexamethasone, ceftriaxone and vancomycin

C. Begin dexamethasone, ceftriaxone, vancomycin, INH, RIF, ETH, PZA

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CNS Tuberculosis

PRESENTATION
Three stages: Prodromal, Meningitic, Paralytic

DIAGNOSIS
Lumbar puncture: OP normal or high
CSF: Lymphocytic pleocytosis, elevated protein, low glucose
Send off the 4th tube, 6ml+
Smear, Culture (70%)
PCR

TREATMENT
Chemotherapy 9-12 months
Steroids

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>
## Diagnosis of TB in the CSF

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

### Sensitivity

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

**Lewinsohn CID 2017**

<table>
<thead>
<tr>
<th></th>
<th>Gene Xpert</th>
<th>Xpert Ultra</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>43</td>
<td>70</td>
<td>43</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 1st 3 mo</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) 10mg/kg 25 mg/kg (2gm) 20mg/kg (1200mg) 20mg/kg (2gm)</td>
<td>INH RIF 5mg/kg (300mg) 10mg/kg</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 20mg/kg</td>
<td>INH RIF 5mg/kg (300mg) 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>&lt;br&gt;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%)
Dexamethasone in CNS TB

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

Cochrane Database Syst Rev. 2008
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.

Nahid CID 2016;63(7):e147–95
TB meningitis in Children

<table>
<thead>
<tr>
<th>American Academy of Pediatrics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. An initial 4-drug regimen of INH, RIF, PZA, and an aminoglycoside or ethionamide for 2 months</td>
</tr>
<tr>
<td>2. Followed by 7–10 months of INH and RIF</td>
</tr>
</tbody>
</table>
Miliary TB in a newborn
Early Clues in disseminated TB
Disseminated Tuberculosis

**PRESENTATION**
Primary or secondary hematogenous infection
Insidious, cryptic fever, weight loss
Rare: ARDS, DIC, pancytopenia

**DIAGNOSIS**
CXR often atypical or normal
PPD and sputum negative in up to 50%
PCR

**TREATMENT**
Chemotherapy 6 months
Extend therapy for CNS/bone joint disease
XPERT MTB RIF in XPTB diagnosis Meta-analysis

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>XPERT MTB/RIF Sensitivity</th>
<th>XPERT MTB/RIF 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 (Ultra*) as the initial test for XPTB. CDC/ATS/IDSA recommends NAAT testing on XPTB specimens.

Guidelines recommend measuring ADA and INF-γ levels in fluid when pleural, pericardial, peritoneal, or meningeal TB is suspected.

Lewinsohn CID 2017
XPTB Treatment

- **6 MONTHS OF STANDARD TB TREATMENT IN MOST CASES**
- **Bone/Joint:** consider extending treatment to 9 months
  CNS disease: 9-12 months
- **Dosing is once daily for both the intensive and continuation phases**
**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 mg/day and taper 10 mg per week; total duration of 6 weeks)