Extrapulmonary Tuberculosis

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Disclosures

• Financial ties: none
• Off-label uses: NAAT on extrapulmonary specimens
Sites of Involvement

Lungs
Lymph Nodes
Pleura
Peritoneum
Bones
Brain
Liver/Spleen
Urinary tract
Genitals
Eyes
Skin


Clinical Presentation: Site of Disease

CDC Reported TB Cases by Form of Disease United States, 2015

Pulmonary (68%)
Extrapulmonary (22%)
Lymphatic (40%)
Pleural (16%)
Bone/joint (10%)
Peritoneal (5%)
Genitourinary (5%)
Meningeal (6%)
Other (18%)
Both (10%)
Pulmonary Involvement in EPTB

- 72 EPTB cases, 2003-2004
- CXR abnormal: 35 (49%)
- Sputum collected (spont-or-induced): 57 (79%)
  - AFB smear positive: 5 (9%)
  - AFB culture positive: 12 (21%)
  - CXR abnormal-vs-normal: 23% vs 19%
  - HIV negative, CXR normal: 2/24 culture positive
- Sputum examinations in EPTB patients…may identify potentially infectious cases of TB


Learning Objectives

- List at least 4 extrapulmonary manifestations of TB and potential approaches to confirm the diagnosis
- Explain the need to evaluate patients with extrapulmonary tuberculosis for potential active pulmonary tuberculosis to determine associated risk of transmission
# EPTB Key Issues

- Diagnosis of pulmonary vs EPTB
- Extension of therapy for certain sites of disease
- Paradoxical worsening & IRIS
- Adjuvant treatment with corticosteroids
- Monitoring response to therapy

<table>
<thead>
<tr>
<th>Issue</th>
<th>Pulmonary</th>
<th>Extrapulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillary load</td>
<td>Often high</td>
<td>Usually low</td>
</tr>
<tr>
<td>Imaging</td>
<td>Plain radiography</td>
<td>CT</td>
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<td></td>
<td>Chest CT</td>
<td>MRI</td>
</tr>
<tr>
<td>Diagnostic specimens</td>
<td>Sputum</td>
<td>FNA</td>
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<tr>
<td></td>
<td>Induce sputum</td>
<td>Bx: core/needle, excisional/surgical</td>
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<tr>
<td></td>
<td>BAL</td>
<td>Serous cavity fluids</td>
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<tr>
<td></td>
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<td>Joint fluids</td>
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<td>Gastric aspirate</td>
<td>CSF</td>
</tr>
<tr>
<td>Sampling</td>
<td>Usually multiple</td>
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</tr>
<tr>
<td>Tests</td>
<td>AFB smear/culture</td>
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<td></td>
<td>Nucleic acid amplification</td>
<td>NAAT</td>
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<td>Cytology/histopathology</td>
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<tr>
<td></td>
<td>Cell count &amp; diff</td>
<td>Protein (+/- LDH), glucose</td>
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<td></td>
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<td>ADA, gamma-interferon</td>
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<tr>
<td>Smear/culture pos</td>
<td>Smear+: 50-70%</td>
<td>Smear+: 25-50%; Culture+: 60-70%</td>
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<tr>
<td>Treatment duration</td>
<td>6-9 months usually</td>
<td>Bone &amp; joint: 6-9 months</td>
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<td></td>
<td></td>
<td>Brain: 9-12 months</td>
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<td></td>
<td></td>
<td>Others: 6 months</td>
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<tr>
<td>Corticosteroids</td>
<td>No</td>
<td>Meningitis</td>
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<tr>
<td></td>
<td></td>
<td>Some pericarditis</td>
</tr>
<tr>
<td>IRIS/paradoxical worsening</td>
<td>Rare</td>
<td>Not uncommon</td>
</tr>
<tr>
<td>Response</td>
<td>Mycobacteriology, clinical, imaging</td>
<td>Clinical, imaging</td>
</tr>
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<td>AFB smear/culture NAAT</td>
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<td></td>
<td>ATS/IDSA/CDC 2017 Dx Guidelines</td>
<td>Cytology/histopathology</td>
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<tr>
<td></td>
<td>“At present, NAAT testing on specimens other than sputum is an off-label use of the test.”</td>
<td>Cell count &amp; diff</td>
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<tr>
<td></td>
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<td>Protein (+/- LDH), glucose</td>
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<tr>
<td><strong>Smear/culture pos</strong></td>
<td>Smear+: 50-70%; Culture+: 90%</td>
<td>Smear+: 25-50%; Culture+: 60-70%</td>
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<td><strong>Treatment duration</strong></td>
<td>6-9 months usually</td>
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<tr>
<td><strong>Corticosteroids</strong></td>
<td>Severe respiratory failure</td>
<td>Meningitis</td>
</tr>
<tr>
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</tbody>
</table>
Radiographic Findings EPTB

- Lymphadenopathy with central attenuation, septation (neck, chest, abdomen, pelvis)
- Effusions
- Diskitis osteomyelitis +/- paraspinal abscess
- Enhancement of meninges, peritoneum, pericardium
- Ring enhancing CNS lesions
- Omental stranding, mesenteric adenopathy
- Bowel wall thickening +/- abscess
- Urinary collecting system obstruction +/- renal parenchymal destruction
- Adnexal mass

Typical Findings Extrapulmonary Specimens

- AFB smear: 10-50% sensitive
- AFB culture: 60-90% sensitive
- NAAT 50-75% sensitive
- Necrotizing granulomata
- Protein elevated
  - Pleural/peritoneal (>4-5gm/dL)
  - CSF (>100-500mg/dL)
- Moderately decreased glucose (~40-50mg/dL)
- Pleocytosis
  - Pleural (1,000-5,000 WBC/uL)
  - CSF (100-500/uL)
  - Lymphocyte predominant differential
Case A--Presentation

• 23 y/o male from western Africa
• Headache, malaise for several months
• Ptosis, double vision
• Fever x 2 weeks
• No cough, sputum

Case A—Diagnosis (1a)

- Meningeal enhancement
- Subcortical T2-Flair infarcts
Case A—Diagnosis (1b)

- CSF
  - RBC 0
  - WBC 357
  - Lymphocytes 87%
  - Protein 148
  - Glucose 56 (vs 130 blood)
  - AFB smear neg
  - TB PCR neg
- Serum Na 130
- HIV negative

Meningeal enhancement

Subcortical T2-Flair infarcts

Typical Findings CSF in TBM

- Protein elevated: 100-500mg/dL (may be higher in spinal block)
- Moderately decreased glucose (~25-50mg/dL)
- Pleocytosis: 100-500/uL
- Lymphocyte predominant differential, but can be mixed or neutrophilic early in presentation
- TB PCR sensitivity: ~50% (range 40-75%)
- AFB smear sensitivity: ~10% (higher for tissue biopsy and CSF pellicle)
- AFB culture sensitivity: ~50%
- ADA
Case A—Diagnosis (2)

- Right apical opacity
- Unable to raise sputum
- BAL 2+, PCR+

TBM Clinical Presentation

- Stage I (e.g., headache and fever only)
  - Non-specific symptoms
  - Few or no clinical signs
  - AAOx3
- Stage II
  - Meningismus
  - Drowsiness/lethargy
  - Focal neurologic deficits
- Stage III
  - Stupor/coma/seizures
  - Gross paresis/paralysis
Survival in TB-HIV Meningitis by Stage

Torok, et al. CID 2011;52:1374

Typical Complications TBM

- Pressure of exudate → cranial nerve palsies (e.g., IV, VI, VII), deafness, visual disturbances, other paresis/paralysis
- Hydrocephalus
  - Communicating (furosemide/acetazolamide)
  - Non-communicating (ventriculostomy, shunt)
- Occlusive vasculitis
- SIADH
- Mass effect
- Paradoxical worsening/IRIS
Corticosteroids in TBM

• RCT, double-blinded, age > 14, HIV-pos & neg, N = 542
• Dexamethasone vs placebo
  – Month 1: 0.4mg/kg/d x 7d → 0.3 → 0.2 → 0.1mg/kg/d x 7d
  – Month 2: 4mg qdx 7 → 3 → 2 → 1mg/kg/d x 7d, then off.
• RR death 0.69 (0.52-0.92)
• Severe disability: 18% vs 13% (NS; p = 0.27)
• Adv effects: 9% vs 20% (p = 0.02)


• Prevents death
• Prevents disability in grade I, but not II or III

Corticosteroids in TBM
In General…Yes

• Generally recommended, especially stage II or III
  TBM or paradoxical worsening
• Less clear role in tuberculoma or spinal TBM
• Dexamethasone 0.4mg/kg/d split qid or prednisone
  1mg/kg/d
• 4 weeks at full dose then 4-week taper

ATS/CDC/IDSA 2016 Rx Guidelines
Mortality benefit
Dexamethasone or prednisolone tapered over 6-8 weeks
**Case A—TBM: Treatment**

- HRZE + dexamethasone started
- Fully sensitive (sputum); CSF culture neg
- Glucocorticoid-associated DM; insulin → metformin
- Dexamethasone taper @ 8 weeks (6mg qid →)
- Recurrent headaches @ 2mg/d
- Dexamethasone back up to 4mg/d then taper (x2)
- Cushingoid
- Finally off dexamethasone at 6 months
- Completed 2HRZE + 10HR DOT

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**Response to Therapy**

> ATS/CDC/IDSA 2016 Rx Guidelines:
> ...repeated lumbar punctures should be considered...
Case B--Presentation

- 23 y/o Vietnamese woman
- R neck swelling, pain
- Otherwise well
- No improvement with amoxicillin/clavulanate

Case B—Diagnosis (1)

- 23 y/o Vietnamese woman
- R neck swelling, pain
- Otherwise well
- No improvement with amoxicillin/clavulanate
- CT neck: ~3cm hypodense LN with peripheral enhancement
Case B—Diagnosis (2)

- 23 y/o Vietnamese woman
- R neck swelling, pain
- Otherwise well
- No improvement with amox/clav
- CXR normal
- CT neck abnormal
- FNA 2+ AFB
- No PCR results
- Bartonella, toxoplasmosis, and EBV seronegative

Case B—Treatment

- 23 y/o Vietnamese woman
- R neck swelling, pain
- CT abnormal; CXR normal
- FNA 2+ AFB
- PCR not done
- Starts HRZE 7/7
- MTB isolated, INH mono-res
- Paradoxical worsening during months 2-3
- Completed 6RZE 7/7
LN TB: Paradoxical Worsening

- Enlarging, new, or draining LNs
- 20-25% of HIV-negative LN cases
- Median onset: 46 days (IQ: 34-111 days)
- Granulomata, AFB+, culture-negative
- Median duration: 69 days
- Robust response to MTB with treatment and release of antigens
- NSAIDs, corticosteroids, aspiration (none evidence based)


Case C--Presentation

- 32 y/o Ukrainian male
- L chest pain, dyspnea, fever, fatigue x3wk
- Lost 3 kg
- No cough, sputum
Case C—Diagnosis (1)

• 32 y/o Ukrainian male
• L chest pain, dyspnea, fever, fatigue x3wk
• Lost 3 kg
• No cough, sputum
• Moderate L effusion
• Compression LLL; otherwise minimal lung abnormalities

Case C—Diagnosis (2)

• 32 y/o Ukrainian male
• L chest pain, dyspnea, fever, fatigue x3wk
• Lost 3 kg
• No cough, sputum
• Moderate L effusion
• 300mL straw-colored fluid
• Protein 5.2gm/dL
• WBC 1200, L 73%, M 14%, P 13%
• AFB smear and TB PCR neg
Pleural Effusion Evaluation Sensitivity

<table>
<thead>
<tr>
<th>Specimen Cultured</th>
<th>AFB Culture Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum only</td>
<td>48%</td>
</tr>
<tr>
<td>Fluid only</td>
<td>63%</td>
</tr>
<tr>
<td>Sputum + Fluid</td>
<td>79%</td>
</tr>
</tbody>
</table>


Pleural Biopsy

- Closed
  - Up to 40% of specimens contain no pleural tissue
  - Image guided gaining favor
  - Sensitivity (pathology + culture): 80-90%
  - Thoracoscopy/VATS: sensitivity approaches 100%


Case C--Pleural TB Rx

- 32 y/o Ukrainian male
- Lymphocytic exudative effusion
- **Sputum AFB smr/PCR neg**
- Necrotizing granulomata on pleural biopsy; no AFB seen.
Pleural Fluid ADA
Low Incidence Setting

- N=338 patients
- Lymphocytic exudative
- 7 pleural TB cases
- Typical cut-off: >40
- Sensitivity: 85%
- Specificity: 90%
- PPV: 85%
- NPV: 99%


ADA Limitations

- False negatives
  - Early disease
  - Advanced age
  - Smokers
- False positives
  - Non-TB empyema, parapneumonic effusions
  - Mesothelioma, lung and hematologic malignancies
  - Rheumatologic conditions

We conclude that commercial IGRA s, performed either on whole-blood or pleural fluid samples, have poor diagnostic accuracy in patients suspected to have TPE.


Case C--Pleural TB Rx

- 32 y/o Ukrainian male
- Lymphocytic exudative effusion
- Sputum AFB smr/PCR neg
- Declines pleural biopsy
- Start HRZE 7/7
- Pleural fluid/tissue AFB cx = MTB
- Fully sensitive
- Sputum AFB cultures negative
- Continues HRZE 7/7 DOT
- Plan: 2HRZE 7/7 +4HR 3/7 DOT
### Other Serous Compartment TB

<table>
<thead>
<tr>
<th></th>
<th>Pericardial</th>
<th>Peritoneal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>Chest pain</td>
<td>Abdominal pain,</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>distension, anorexia</td>
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<tr>
<td></td>
<td>Narrowed pulse pressure</td>
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<tr>
<td><strong>Radiography</strong></td>
<td>Enlarged cardiac shadow</td>
<td>Ascites, fat stranding,</td>
</tr>
<tr>
<td></td>
<td>Effusion (US/CT)</td>
<td>adenopathy, studding</td>
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<tr>
<td><strong>Specimens</strong></td>
<td>Pericardiocentes</td>
<td>Paracentesis</td>
</tr>
<tr>
<td></td>
<td>PCR, AFB smr/cx, cell count</td>
<td>Peritoneal biopsy</td>
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<tr>
<td></td>
<td>diff, chemistry, ADA, IGRA</td>
<td></td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>Standard</td>
<td>Standard</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Sometimes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Corticosteroids in TB Pericarditis

- RCT, 2/3 HIV-pos, N=1400 adults
- 2x2 design: prednisolone, *M. indicus pranii* immunotherapy, placebo
- Prednisolone 120mg/dx7d→90→60→30→15→5mg/d
- No difference in death+tamponade+constrictive pericarditis
  - HR 0.95 (0.77-1.81; 24% vs 26%; p=0.66)
- Constrictive pericarditis reduced: 4.4% vs 7.8%; HR 0.56 (0.36-0.87; p=0.04)
- Hospitalization reduced: 21% vs 25%; HR 0.79 (0.63-0.99; p=0.04)
- Cancer increased: 1.8% vs 0.6%; HR3.27 (1.03-13.24)—mostly HIV
- *M. indicus*: no benefit, similar increased risk of cancer

***Editorial & Prevailing Guidelines:***

- Routine use should not be endorsed
- Yes if high risk for constriction
- Large effusion, high cell counts, early signs of constriction

*Mayosi, et al. NEJM 2014;371:1121-30*
*Chaisson, Post. NEJM 2014;371:1155-57*
*ATS/CDC/IDSA 2016 Rx Guidelines*
Case D--Presentation

- 36 y/o Filipino male
- Returned from 3 month stay back home about 6 months ago where he was caring for his dying grandfather.
- DM-II
- Gradually increasing mid-back pain for 2-3 months, night sweats; now lower extremity weakness and paraesthesiae
- No cough

Case D—Diagnosis (1)

- 36 y/o Filipino male with DM
- Back pain, fever
- CXR normal
- T12-L1 osteomyelitis-diskitis with spinal cord compression
- No psoas abscess
Case D—Diagnosis (2)

- 36 y/o Filipino male with DM
- Back pain, fever
- Abnl MRI c/w TB
- Surgical debridement, anterior corpectomy with cage placement, grafting, and posterior fixation
- Necrotizing granulomata w/o AFB
- TB PCR neg
- AFB cx pending
- QFT indeterminate (low mitogen)

Case D--Spinal TB Rx

- 36 y/o Filipino male with DM
- T12-L1 spinal TB with cord compression
- Surgical debridement with cage and posterior fixation
- Started HRZE+B6
- MTB fully sensitive from surgical bx
- Completed 2HRZE+7HR
### Other Sites of EPTB

<table>
<thead>
<tr>
<th>Site</th>
<th>Diagnostics</th>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>Urine AFB culture</td>
<td>Standard</td>
<td>Flank pain+fever Hematuria Sterile pyuria</td>
</tr>
<tr>
<td></td>
<td>Urine PCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biopsy specimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital tract</td>
<td>Biopsy specimens</td>
<td>Standard</td>
<td>Female&gt;male Tubes, ovaries Epididymis</td>
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<tr>
<td>Liver/spleen</td>
<td>LFTs: mild cholestatic profile</td>
<td>Standard</td>
<td>Not uncommon in disseminated* TB, especially miliary</td>
</tr>
<tr>
<td></td>
<td>Biopsy (rare)</td>
<td></td>
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<tr>
<td>Ocular</td>
<td>Exam Positive TST/IGRA</td>
<td>“Standard”</td>
<td>Anterior uveitis Pan uveitis/choroiditis TB bacilli or hypersensitivity Choroidal nodules</td>
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<tr>
<td></td>
<td>Exclusion of other causes</td>
<td>+/- ophthalmic corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aqueous/vitreous fluid (rare)</td>
<td></td>
<td></td>
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<tr>
<td>Erythema induratum</td>
<td>Biopsy: panniculitis</td>
<td>??</td>
<td>Hypersensitivity (not disease) Some PCR+ No organisms</td>
</tr>
</tbody>
</table>

*disseminated = involvement of two anatomically non-contiguous sites

### EPTB Summary

- LN, pleura most common; any site can be affected
- CNS TB can be a medical/surgical emergency
- Look for concurrent pulmonary TB
- Dx: imaging→sampling→mycobacteriology+
- Rx: CNS 9-12mos, bone 6-9mos, others 6mos
- Corticosteroids: TBM, ?tuberculoma, ?pericardial
Discussion

Questions/Comments?

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Radiographic Findings—CNS TB

• Basilar meningeal enhancement
• Hydrocephalus
• Ring enhancing lesions
• Granulomata
• Cerebral infarctions
• Edema and/or mass effect
• Encephalomalacia

Seemingly more useful for diagnosis than grading clinical severity or predicting outcome

CNS TB Evaluation Components

• MRI brain
• Plain CXR (+/- CT CAP)
• CSF (+/- brain tissue—rarely needed)
• Sputum x3 (AFB smr/cx x3; PCR x 1-2)
• HIV
• QFT +/- TST ??

Note: Negative TST or QFT results never exclude active TB and indeterminate or false negative results are common in hospitalized patients.
Basilar Meningeal Enhancement


Hydrocephalus

Tuberculoma


Multiple Tuberculomata
Abscess with Mass Effect
CSF Characteristics

California Encephalitis Project

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CNS TB</th>
<th>HSV-1</th>
<th>Enterovirus</th>
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<tbody>
<tr>
<td>No. Cases</td>
<td>20</td>
<td>39</td>
<td>44</td>
</tr>
<tr>
<td>CSF leukocytes per ml, median</td>
<td>201</td>
<td>47</td>
<td>85</td>
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<tr>
<td>CSF protein, mg/dl, median</td>
<td>174</td>
<td>71</td>
<td>60</td>
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<tr>
<td>CSF glucose, mg/dl, median</td>
<td>35</td>
<td>69</td>
<td>67</td>
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- All 20 CNS TB cases: culture positive
- 4/17 (24%) CSF TB PCR positive

c/o Timothy Dellit, MD

CNS Penetration of TB Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC (ug/mL)</th>
<th>Target serum (ug/mL)</th>
<th>Peak CSF (ug/mL)</th>
<th>CSF-MIC</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (H)</td>
<td>0.025-0.05</td>
<td>3-5</td>
<td>3-5</td>
<td>&gt;10:1</td>
<td>Good</td>
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<tr>
<td>Rifampin (R)</td>
<td>0.005-0.20</td>
<td>8-24</td>
<td>0.5</td>
<td>&gt;2:1</td>
<td>Inflamed—good Otherwise—fair</td>
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<td>Pyrazinamide (Z)</td>
<td>12.5</td>
<td>20-40</td>
<td>25-40</td>
<td>&gt;2:1</td>
<td>Good</td>
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<tr>
<td>Ethambutol (E)</td>
<td>1.0</td>
<td>2-6</td>
<td>0.5</td>
<td>&lt;1:1</td>
<td>Inflamed-fair Otherwise-poor</td>
</tr>
<tr>
<td>Streptomycin (S)</td>
<td>0.4-10</td>
<td>35-45</td>
<td>1-2</td>
<td>~1:1</td>
<td>Inflamed-fair Otherwise-poor</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>0.25</td>
<td>8-12</td>
<td>--</td>
<td>10:1</td>
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<tr>
<td>Moxifloxacin</td>
<td>--</td>
<td>3-5</td>
<td>--</td>
<td>--</td>
<td>“Good”-animals</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>0.6-2.5</td>
<td>1-5</td>
<td>1</td>
<td>~1:1</td>
<td>Good</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>--</td>
<td>20-35</td>
<td>10-20</td>
<td>--</td>
<td>Good</td>
</tr>
<tr>
<td>Linezolid</td>
<td>--</td>
<td>12-24</td>
<td>--</td>
<td>--</td>
<td>Fair (?)</td>
</tr>
<tr>
<td>PAS</td>
<td>--</td>
<td>20-60</td>
<td>--</td>
<td>--</td>
<td>“Poor”</td>
</tr>
</tbody>
</table>
"Intensified" Anti-CNS TB Rx


<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>2wk Dose</th>
<th>8wk Dose</th>
<th>26wk Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH (5mg/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIF</td>
<td>13mg/kgIV</td>
<td></td>
<td>10mg/kg</td>
<td></td>
</tr>
<tr>
<td>PZA (25mg/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMB (750mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or MOX (400 or 800mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WEEKS</td>
<td>0</td>
<td>2wk</td>
<td>8wk</td>
<td>26wk</td>
</tr>
</tbody>
</table>

Not to scale

---

"Intensified" Anti-CNS TB Rx-2

*Heemskerk, et al. NEJM 2016;374:124-134*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>2wk Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH (5mg/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIF (15mg/kg)</td>
<td></td>
<td>10mg/kg</td>
<td>2</td>
</tr>
<tr>
<td>PZA (25mg/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMB (20mg/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEV (20mg/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEV (20mg/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONTHS</td>
<td>0</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

Initial | Continuation
“Intensified” Anti-CNS TB Rx-2

Heemskerk, et al. NEJM 2016;374:124-134

• N=60 enrolled
• RIF AUC increased 3x
• MOX 400→800 AUC ↑2x

“Intensified” Anti-CNS TB Rx-2

Heemskerk, et al. NEJM 2016;374:124-134

• N = ~800 enrolled
• No difference in mortality
• No impact on HIV+ or HIV-
• Marginally significant reduced mortality in INH-resistant cases (24% vs 39%; p=0.06)
Dex benefit is LTA4H Genotype dependent

Tobin, Ramakrishnan, Thwaites  Cell 2010,  Cell 2012

LTA4H SNP rs17525495
Low Inflammation (CC): Harm from dex
High Inflammation (TT): Benefit from dex

Goldilocks Phenomenon

Slide c/o Thomas Hawn, MD, PhD

Pleural TB: pleural fluid analysis (Guidelines)

- NAAT should be measured (conditional recommendation, very low-quality of evidence: NAAT sensitivity 55%)
- ADA levels and free IFN-gamma levels should be measured (conditional recommendation, low-quality of evidence)
  - Sensitivity ~70%, specificity ~80%
  - Caution:
    - Neither ADA nor IFN-γ levels are standardized
    - Provide only supportive evidence

Slide c/o Masa Narita