Central Nervous System Tuberculosis

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Objectives

• At the end of this presentation you will be able to:
  • Be able to describe the clinical presentation of TB meningitis and other CNS TB
  
  • Discuss the diagnostic evaluation for TB meningitis and some of the limitations
  
  • Discuss differences in the approach to treatment of TB meningitis compared to pulmonary TB
Percentage of extrapulmonary cases among new and relapse TB cases

- (CNS) involvement of tuberculosis (TB) accounts for approximately 5 to 10% of all extrapulmonary TB (EPTB) cases and approximately 1% of all TB cases
- Estimated 64,000-100,000 individuals with TB meningitis globally in 2017
Pulmonary Involvement in Extrapulmonary TB (EPTB)

- 72 EPTB cases, 2003-2004
- CXR abnormal: 35 (49%)
- Sputum collected (spontaneous-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

9,105 individuals with active TB
87 with TB meningitis (4.3%)
TB Meningitis: Clinical Presentation

Stage I
- Headache and fever only
- Non-specific symptoms

Stage II
- Meningismus
- Drowsiness/lethargy
- Focal neurologic deficits

Stage III
- Stupor/coma/seizures
- Gross paresis/paralysis
Typical Complications
TB Meningitis

- Pressure of exudate → cranial nerve palsies
- Hydrocephalus
- Occlusive vasculitis and infarction (30-40%)
- SIADH
- Paradoxical worsening/IRIS
- Seizures
- Death/permanent disability in up to 50%
Radiographic Findings in CNS TB

- Basal meningeal enhancement (in up to 90%)
- Hydrocephalus (in ~66%)
- Infarction (in >50%)
- Tuberculoma (in ~30%)

• Important to evaluate for pulmonary disease

hyperintense leptomeninges: white arrow narrowed sulcal spaces, black arrow).

Typical Findings CSF in TB Meningitis

- **Protein elevated:** 100-500mg/dL (may be higher in spinal block)
- **Moderately decreased glucose:** (~25-50mg/dL)
- **Pleocytosis:** 100-500/uL
- **Lymphocyte predominant, but can be mixed or neutrophilic early in presentation**

- **TB PCR sensitivity:** ~50% (range 40-75%)
- **AFB smear sensitivity:** ~10%
- **AFB culture sensitivity:** 5-50%
<table>
<thead>
<tr>
<th>Issue</th>
<th>Pulmonary</th>
<th>CNS TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacillary load</strong></td>
<td>Often high</td>
<td>Usually low</td>
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<tr>
<td><strong>Imaging</strong></td>
<td>Plain radiography</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>Chest CT</td>
<td>MRI</td>
</tr>
<tr>
<td><strong>Diagnostic specimens</strong></td>
<td>Sputum</td>
<td>CSF; biopsy rarely done</td>
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<tr>
<td></td>
<td>Induce sputum</td>
<td></td>
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<tr>
<td></td>
<td>BAL</td>
<td></td>
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<tr>
<td></td>
<td>Post bronchoscopy</td>
<td></td>
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<tr>
<td></td>
<td>Gastric aspirate</td>
<td></td>
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<tr>
<td><strong>Sampling</strong></td>
<td>Usually multiple</td>
<td>Usually single</td>
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<tr>
<td><strong>Tests</strong></td>
<td>AFB smear/culture</td>
<td>AFB smear/culture</td>
</tr>
<tr>
<td></td>
<td>Nucleic acid amplification</td>
<td>NAAT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cell count &amp; diff</td>
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<tr>
<td></td>
<td></td>
<td>Protein (+/- LDH), glucose</td>
</tr>
<tr>
<td><strong>Smear/culture positive</strong></td>
<td>Smear+: 50-70% Culture+:90%</td>
<td>Smear+: &lt;10%; Culture+:5-50%</td>
</tr>
<tr>
<td><strong>Treatment duration</strong></td>
<td>6-9 months usually</td>
<td>9-12 months</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>IRIS/paradoxical worsening</strong></td>
<td>Rare</td>
<td>Not uncommon</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>Mycobacteriology, clinical, im</td>
<td>Clinical, imaging</td>
</tr>
</tbody>
</table>
Patient #1

- 28 year old woman, originally from Mexico, presented to her primary care provider with cough for 2 months
- Urgent care visit 3 days after that visit
  - Continued cough, CXR obtained...
  - Given azithromycin and discharged from the ED.
5 months later: repeat PCP visit:
- continued cough, no relief with albuterol
- 8 lb. weight loss: BMI 18.6.
- QVAR and Claritin were added to her albuterol.
- Chest radiograph findings were noted → referred to pulmonary, CT chest ordered.
Patient #1

- One month later: seen in the ED
  - continued chronic cough, tachycardic to 115. Was discharged

- Two days after ED visit in pulmonary clinic:
  - Working diagnosis of possible bronchiolitis, bronchoscopy planned but she didn’t have the funds to cover to copay
Patient #1

- 3 weeks after pulm visit, 7 months into her illness
  - Went to the ED with headache for 7 days, fever, nausea/vomiting and body aches and sore throat
    - DX ➔ strep throat
    - RX ➔ azithromycin
  - Chest x-ray was noted to have “no acute findings.”
- Went back twice in one week: persistent headaches, nausea vomiting and now photophobia, visual disturbances
  - DX ➔ tension headache
  - RX ➔ follow up with her primary care provider
Patient #1

• Family took her to another hospital
  • Somnolence, confusion
  • Continued nausea/vomiting
• MRI/brain: diffuse focal flair hyperintensity; diffuse leptomeningeal enhancement compatible with meningitis.
• LP: WBC 149, t prot 152, glucose 14
  • *M. tuberculosis* PCR positive

• Bronchoalveolar lavage AFB smear +, probe + *Mycobacterium tuberculosis*.
• Started on TB treatment with isoniazid, rifampin, pyrazinamide and ethambutol and steroids
• Course complicated by development of seizures, several days in the ICU

• Profoundly debilitated at discharge
CNS TB: Key Aspects of Treatment

- Diagnosis of pulmonary disease
- Extension of therapy
- Paradoxical worsening & IRIS
- Adjuvant treatment with corticosteroids
- Monitoring response to therapy
### First-line drugs for treatment of drug sensitive TBM in adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>WHO-recommended daily dose</th>
<th>WHO-recommended duration</th>
<th>CSF penetrance (CSF:plasma concentration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>10 mg/kg (range 8–12 mg/kg); max 600 mg</td>
<td>12 months</td>
<td>10–20%</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>5 mg/kg (range 4–6 mg/kg); max 300 mg</td>
<td>12 months</td>
<td>80–90%</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25 mg/kg (range 20–30 mg/kg)</td>
<td>2 months</td>
<td>90–100%</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg/kg (range 15–20 mg/kg)</td>
<td>2 months</td>
<td>20–30%</td>
</tr>
</tbody>
</table>

### Second-line drugs for treatment of TBM in adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>WHO-recommended daily dose</th>
<th>WHO-recommended duration</th>
<th>CSF penetrance (CSF:plasma concentration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td>10–15 mg/kg</td>
<td>Throughout treatment</td>
<td>70–80%</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>Throughout treatment</td>
<td>70–80%</td>
</tr>
<tr>
<td>Amikacin</td>
<td>15 mg/kg; max 1 g. IV or IM.</td>
<td>Intensive phase only</td>
<td>10–20%</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>15 mg/kg; max 1 g. IV or IM.</td>
<td>Intensive phase only</td>
<td>10–20%</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15 mg/kg; max 1 g. IV or IM.</td>
<td>Intensive phase only</td>
<td>No data (probably very low)</td>
</tr>
<tr>
<td>Ethionamide or prothionamide</td>
<td>15–20 mg/kg; max 1 g.</td>
<td>Throughout treatment</td>
<td>80–90%</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>10–15 mg/kg; max 1 g.</td>
<td>Throughout treatment</td>
<td>80–90%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg</td>
<td>Throughout treatment</td>
<td>30–70%</td>
</tr>
</tbody>
</table>

Other drugs used in treatment of multi-drug-resistant TB but of uncertain benefit in TBM

- **Clofazimine**
  - 100 mg OD
  - No recommended duration
  - Limited data (probably low)

- **p-Aminosalicylic acid**
  - 200–300 mg/kg
  - No recommended duration
  - No data (probably very low)

- **Bedaquiline**
  - Not determined
  - New drug. Limited availability.
  - Probably very low (but data from one patient only)

- **Delamanid**
  - Not determined
  - New drug. Limited availability.
  - No data
TB Meningitis treatment

- Current IDSA/ATS recommendations are for isoniazid, rifampin, pyrazinamide, ethambutol, 5-7 days per week
  - Ethionamide is substituted for ethambutol in children
- Largest trial of 817 patients *failed* to show decreased mortality with an “intensified regimen” of higher dose rifampin (15mg/kg) and use of a fluoroquinolone

- No comparative trial data on duration of 6 vs. 9 months for meningitis

Heemskerk AD, NEJM 2016
Nahid P. CID 2016
Corticosteroids in TB Meningitis

- RCT, double-blinded, age>14, N=542
- Dexamethasone vs placebo
- RR death 0.69 (0.52-0.92), p=0.01
- Severe disability: 18% vs 13% (NS; p=0.27)
- Adverse effects: 9% vs 20% (p=0.02)

Corticosteroids in TB Meningitis

- Dexamethasone 0.4mg/kg/d split every 6 hours or prednisone 1mg/kg/d
  - Tapered over 6-8 weeks
- Less clear role in tuberculoma or spinal TBM
Early antiretroviral therapy (ART) does not improve outcomes in HIV-positive patients with TB meningitis

- N=253 patients
- Immediate (less than 2 weeks) ART was not associated with decreased mortality
- Increased adverse events in the immediate ART arm

Torok, E.M. et al. CID 2011
Treatment course of patient #1

- Headaches began to worsen as steroids were tapered:
- Hospitalized again:
  - Worsened inflammatory findings on MRI and in CSF
  - Stopped PZA and added moxifloxacin
- Moxifloxacin continued until repeat CSF cultures finalized as negative
- Slower steroid taper, added non-steroidal anti-inflammatory agent
- Gradually improved and completed 12 months of daily therapy
- Considered to have a full recovery
Patient #2: 29 y/o with fever

- Originally from Chicago, healthy
- **Late July** – developed fevers and headache
- **Early August** – went to an Urgent Care was given doxycycline
- **Late August** – went to an ED and was treated with levofloxacin
- **Mid September** – underwent BAL and biopsy that were non-diagnostic
Patient #2: 29 y/o with fever

- He woke up confused so his partner took him to a hospital
- WBC 7.9 / BMP – normal / HIV negative
- ESR 8, CRP 7.6
- CSF:
  - WBC 830 (73% Neut., 10% Lymph.); RBC 2
  - Protein 241
  - Glucose 15
- Ceftriaxone, Vancomycin, ACV and Dexamethasone (10 mg q6hrs)
29 y/o with fever

Extensive work-up **negative for the following:**

- HIV
- Bacterial and viral cx, syphilis serology
- HSV, Enterovirus, VZV, CMV, and EBV PCRs, WNV IgG & IgM, Crypto Ag
- Urine Strep pneumo Ag and Legionella Ag
- Urine Histo Ag, Cocci serology
- Resp viral PCR panel, VZV serum serology
- Lyme Ab panel
- **Quantiferon TB Gold in-Tube**
Patient #2: 29 y/o with fever

- He got **progressively worse** despite broad empiric treatment and began having **strokes**

He died in the hospital after a few weeks in October

Cultures from BAL and spinal fluid grew TB in late October
Patient #2: 29 y/o with fever-lessons learned

• Unclear risk factors—spent time in Spain but no other travel, no travel with his family when he was a child

• In retrospect had upper lobe infiltrates that responded to fluoroquinolones

• Likely had some partial response to use of corticosteroids in the beginning of his hospital course when on treatment for bacterial meningitis
Patient #3

24 year old graduate student

Hospitalized with several weeks of cough, night sweats and fevers

- Overseas screening with 0 mm TST
- No prior CXR
- Denies other localizing symptoms
Patient #3

- HIV negative
- Sputum AFB smear+, initiated on I/R/E/Z daily
  - Cultures eventually grew drug-susceptible *M. tuberculosis*
- Urine culture positive for *M. tuberculosis*
- Converted sputum culture at one month with excellent clinical response
- After 8 weeks of I/R/E/Z daily, changed to I/R twice weekly
Patient #3

• 3 months into therapy he presented with new onset seizures
• LP results:
  • WBC 0
  • RBC 2
  • glucose 52 mg/dL (ref 50-75)
  • protein 78 mg/dL (ref-12-60)
  • MTB PCR NAAT neg
  • AFB smear/culture negative at 6 weeks
• Toxo IgG/IgM neg
3 months into TB treatment
Patient # 3 questions

- Is this paradoxical IRIS or failure of twice weekly regimen to control disseminated disease?

- Should his therapy be modified by:
  - Resuming 4 drugs or new drugs?
  - Increasing frequency and/or doses?
  - Using corticosteroids?
CNS Tuberculoma treatment

- Debate regarding the optimal regimen and duration
  - IDSA/ATS: no reference to treatment of CNS tuberculoma, referred back to management of TB meningitis, duration of 9-12 months
  - British Guidelines: 12 months duration
  - Other Expert consensus: “four anti-tuberculous drugs for 18 months or until the tuberculoma resolves”
    - Davis A, et al. Curr Treat Options Neurol, 2018
Patient #3

- Continued on INH+RIF but increasing to TIW
- Anti-seizure treatment with Keppra
- Prednisone taper over 2 months
- Traveled outside of the US to parent’s home, given Rifamate SAT months 5 & 6
- No other symptoms or seizures until the end of the 6th month of TB treatment:
  - Notes mild difficulties with word finding
  - Reports adherence to TB treatment while traveling
6 months into TB treatment (4 months DOT, 2 months SAT)
Patient #3 questions

Does this represent microbiologic treatment failure? What are the risks/benefits of biopsy in an attempt to obtain an isolate?

Does this represent inadequate treatment? What is the role for therapeutic drug monitoring or alternative drugs?

Does this represent the persistence of inflammatory response alone despite microbiologic cure?
Patient #3

• Lesion near motor strip therefore biopsy risked permanent neurologic deficits
  • Discussed with patient, consensus was to defer at this time, revisit if clinical worsening
• Prednisone restarted, no change in TB treatment
  • Symptoms resolved
• MRI repeated one month later
7 months into TB treatment s/p one month of corticosteroids

January 2014

February 2014

Continued to do well clinically
Tapered prednisone by early April and then...Two more seizures (May and June of 2014)
11 months of TB treatment (9 months DOT, 2 months SAT)
Patient #3

• Continued TIW until completing one year of DOT
  • Thereafter switched to rifamate daily

• Repeat MRI at 16 months of treatment showed improvement in largest lesion, few new smaller lesions

• Continued TB treatment for an additional 3 months and repeated MRI 1/2015:
End of Treatment: 19 months

MRI:
- overall mild improvement of disease
- decreased size and enhancement of several ring-enhancing lesions
- overall slight decrease in the edema surrounding the tuberculomas
- No new lesions visualized
Patient #3 Summary

- 24 year old man who presented with miliary/disseminated TB, found to have CNS disease 3 months into treatment
  - Slowly exhibited radiographic and clinical improvement
  - Unclear if new lesions appearing while the majority improving were indicative of continued infection or inflammatory response
  - Completed 19 months of TB treatment, currently doing well
- Optimal treatment course for CNS tuberculomas remain uncertain
**Summary**

<table>
<thead>
<tr>
<th>TB meningitis is a subacute, devastating disease which remains difficult to diagnosis and manage</th>
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<tbody>
<tr>
<td>• Important to evaluate for pulmonary disease</td>
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<tr>
<td>• Standard treatment is with INH, PZA, EMB and rifampin for adults</td>
</tr>
<tr>
<td>• Adjunctive corticosteroids can improve outcomes</td>
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<tr>
<td>• The optimal timing for antiretroviral therapy for HIV-positive individuals with TB meningitis is likely around 4 weeks</td>
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</tbody>
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<tr>
<th>CNS tuberculomas may be clinically silent, manifest later in treatment for TB disease of other organs</th>
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<tr>
<td>• No data on optimal duration of treatment</td>
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<td>• Likely 12 months is of benefit but consultation with experts and an individualized approach is recommended.</td>
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</table>
Questions?