TB Meningitis Can be a Real Headache
Dr. Manasa Velagapudi MBBS
Dr. Lisa Armitige MD, PhD
November 22, 2019

Medical Consultant Meeting
November 22, 2019
San Antonio, Texas

Friday, November 22, 2019

Medical Consultant Meeting

Speakers:
Barbara J. Seaworth, MD; Heartland National TB Center
Dick Brostrom, MD; Centers for Disease Control and Prevention
Manasa Velagapudi, MBBS; Creighton University Medical Center
Lisa Y. Armitige, MD, PhD; Heartland National TB Center
Bob Belknap, MD; Denver Health and Hospitals Metro TB Program
Jim McAuley, MD; Whiteriver Indian Health Services
Janice Louie, MD; San Francisco Department of Public Health

Today’s presenters, CME Committee, staff and planning committee have indicated they have no commercial affiliations to disclose.
TB Meningitis
Can be a Real Headache

Dr. Manasa Velagapudi MBBS
Assistant Professor
Creighton University School of Medicine, Nebraska

Dr. Lisa Armitige MD, PhD
Heartland National Center

HPI –Initial presentation

• 31-year-old male

• Presented with acute onset of slurred speech, left facial droop, altered mental status
  – 3 days of occipital headache
  – Resolved by arrival

• Absence seizure, focal LUE weakness

• CT head-nonspecific

• Hypotension, requiring ICU admission

• Profoundly hyponatremic
HPI – Initial presentation

• Weight loss of 8-10 kg over 8 months.

• Past Medical History:
  – history of positive PPD
  – didn’t finish INH therapy - elevated LFTs
  – Gastritis

• Home medications: None

• Allergies: NKDA

Social history

• From Nepal

• Immigrated to the US 4 years ago, last trip back to Nepal was 2 years ago

• Divorced, currently lives in the home of his aunt (with her husband and their daughter)

• No ill contacts
Social history (cont)

• Nonsmoker, no known IV drug use.

• His aunt reports substantial ETOH consumption history - sober since 3-4 years ago

• He works in IT field

• No pets in the household

Physical Exam

• Ht: 167.6 cm 5’ 6”

• Wt: 54 kg (119 lb.) – BMI 19.21 kg/m²

• Physical exam:
  – Eyes: No scleral icterus
  – Neurologic: opens eyes to voice, no involuntary movements speech clear, no facial asymmetry, no focal motor deficits
  – Remainder of exam unremarkable
Laboratory workup – At presentation

- WBC 8.8
- Hgb 14.0
- HCT 41.1
- PLT 284

- NA 123
- Cl 110
- K 3.6
- CO2 25
- BUN 12
- Cr 0.81
- Glucose 122

- Ca 8.8
- TP 8.3
- ALB 3.2
- AST 19
- ALT 24
- AP 184
- T. Bil 0.7
Pathogenesis

- Rich and McCordock published an autopsy study of TBM patients
  - Observed granulomas rupturing into the subarachnoid space in nearly all the cases (Rich focus)

- Exudate at the base of the brain (basilar meningitis), histologically, includes erythrocytes, mononuclear cells, neutrophils and bacilli

- Vasculitis
  - Middle cerebral arteries and Circle of Willis vessels most often affected
  - Cerebral infarct found in 1/3 of patients

- TNF-α levels show some correlation with disease severity
Clinical Presentation

• Often present with the classic meningitis symptoms
  • fever, headache and meningismus
  • focal neurological deficits, behavioral changes, and alterations in consciousness

• The presence of active pulmonary tuberculosis on chest X ray ranges from 30 to 50% in recent series

• Patients co-infected with HIV do not appear to have an altered presentation of TBM

• Hyponatremia is common (SIADH or cerebral salt wasting)

• Clinical presentation at diagnosis is the strongest predictor of outcome

Outcomes

| TABLE 1. British Medical Research Council clinical criteria for the severity of TBM® |
|------------------|------------------|
| Stage/grade | Classic criteria |
| I | Fully conscious and no focal deficits |
| II | Conscious but with inattention, confusion, lethargy, and focal neurological signs |
| III | Stuporous or comatose, multiple cranial nerve palsies, or complete hemiparesis or paralysis |

<table>
<thead>
<tr>
<th>Contemporary criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alert and oriented without focal neurological deficits</td>
</tr>
<tr>
<td>Glasgow coma score of 14-11 or 15 with focal neurological deficits</td>
</tr>
<tr>
<td>Glasgow coma score of 10 or less, with or without focal neurological deficits</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Death or Disability</th>
<th>Death or Severe Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV -</td>
<td>HIV +</td>
</tr>
<tr>
<td>15%</td>
<td>25%</td>
</tr>
<tr>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>50%</td>
<td>80%</td>
</tr>
</tbody>
</table>
Deaths Attributed to TB Disease or TB Treatment, 2016*

9 of every 100 TB patients diagnosed in 2016 died before diagnosis or during treatment

More than 3 of the 9 deaths were attributed to TB disease or TB treatment

*Data available through 2016 only.

Microbiology

• Sputum AFB smear/culture negative

• BAL
  – MTB DNA probe – MTB detected, no rpoB mutations detected
  – AFB smear negative

• LP
  – Colorless, cloudy CSF
  – 238 nucleated cells (83% neutrophils), 13 RBC
  – protein of 175 mg/dL
  – glucose of 10mg/dl

• MTB PCR – positive for MTB on CSF

• AFB culture of BAL and CSF both positive - pan susceptible isolate
Diagnosis of TB Meningitis

- Typical CSF findings
  - Lymphocytes 100-1000 cells/mm³ (first 10 days may have PMN predominance)
  - Elevated protein, decreased glucose

- Clinical and Laboratory findings (pediatric TBM-review and meta-analysis)
  - Leukocytosis: 99.9%
  - CSF lymphocytosis: 97.9%
  - Fever: 89.9%
  - Hydrocephalus: 86.1%
  - CSF AFB smear positivity: 8.9%
  - CSF AFB culture positivity: 35.1%

Diagnosis of TB Meningitis (cont)

- AFB stain:
  - Sensitivity 10-20%
  - Large volume (10 ml), centrifuged, 30 minute examination by an experienced microscopist can increase detection to >80%

- Culture
  - More sensitive, not timely enough to effect decision making

- Xpert
  - 3 studies, found to be about 60% sensitive (enhanced by large volume tap, centrifugation)

- 22% TST/IGRA negative at diagnosis
Susceptibilities

*Mycobacterium tuberculosis* complex

- Ethambutol 5.0 ug/mL  
  Sensitive
- Isoniazid @ 0.1 ug/mL  
  Sensitive
- Pyrazinamide 100 ug/mL  
  Sensitive
- Rifampin 1.0 ug/mL  
  Sensitive

Initial ATT

- Isoniazid  300 mg daily
- Rifampin  600 mg daily
- Pyrazinamide 1000 mg daily
- Ethambutol  800 mg daily
- Pyridoxine  50 mg daily

- Dexamethasone taper over 8 weeks

- His other pertinent current meds:
  - Keppra 750 mg po
  - Omeprazole 20 mg po q daily
  - Acetaminophen 650 mg po q6 prn
MRI brain

Radiographic Findings

• CT or MRI with contrast:
  • basal meningeal enhancement
  • Hydrocephalus (87% in children, 12% in adults)
  • Infarction (28% of patients, 83% MCA distribution)
  • Tuberculomas (contrast will highlight ring-enhancement)

• Findings may worsen initially (immune mediated), has responded to corticosteroids and thalidomide

CT chest

CT abdomen
Imaging

• CT abdomen and pelvis: multiple subcentimeter hypodense lesions within the liver may reflect enhancing dysplastic or degenerative nodules. 9 mm hypodense lesion on bladder, Small abdominal and pelvic ascites. Irregular 9 mm hyperdensity along the right posterolateral urinary bladder.

Hospital course

• Encephalopathy resolved

• No further seizures

• AFB sputum x 3- smear negative

• Extreme weakness

• Discharged to rehab
Follow up – 1 month

• 1 month into therapy-nausea and vomiting
  – Attributed to high dose pyridoxine (500 mg given inadvertently at rehab)
  – Switched back to 50 mg

• Started on Zofran, promethazine

• Persistent nausea- keppra dose was reduced

1 month clinic follow up

• All through this time, great appetite,

• Did not gain weight (remained at 54-56 kg)

• Serum Drug levels:
  – Rifampin level- 5.07 mcg/ml (dose of 600 mg daily)
  – Isoniazid level- 0.54 mcg/ml
4 months later

- Cholecystectomy - resolution of nausea and vomiting
- 1 month after resolution of his symptoms, rechecked serum drug levels
  - Rifampin level <0.50 mcg/ml
  - Isoniazid level 2.10 mcg/ml
- Treatment history:
  - Isoniazid 300 mg po daily with pyridoxine
  - Rifampin 600 mg po daily
  - Finished 2 months of Pyrazinamide & Ethambutol
  - Dexamethasone taper over 8 weeks
- Dr. Seaworth was consulted for assistance
CT Abdomen & Chest

- CT abdomen:
  - Interval decreased size or resolution of multiple hepatic hypo densities.

- CT chest:
  - Significantly improved aeration of the lungs with residual miliary and tree-in-bud nodularity, predominantly within the upper lobes. Findings are consistent with improving miliary tuberculosis.
  - Resolved mediastinal and right hilar lymphadenopathy and pericardial effusion

Repeat LP

- Colorless cloudy CSF
- 48 nucleated cells, 89 % lymphocytes, 13 RBC
- Protein 295 mg/dL
- Glucose 38 mg/dl
- MTB PCR- negative for MTB
- AFB culture and smear- no AFB isolated at 6 weeks
Enhanced/Augmented ATT

- Isoniazid 300 mg
- Rifampin 900 mg
- Pyrazinamide 1500 mg
- Moxifloxacin 400 mg
- Linezolid 600 mg
- Dexamethasone 24 mg
- Aspirin 81 mg

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Cerebrospinal Fluid Drug Concentrations and the Treatment of Tuberculous Meningitis

GORDON A. ELLARD, MICHAEL J. HUMPHRIES, and BRYAN W. ALLEN

National Institute for Medical Research, London, United Kingdom; Ruttonjee Sanatorium, Hong Kong and Department of Bacteriology, Royal Postgraduate Medical School, London, United Kingdom

**TABLE 1**

<table>
<thead>
<tr>
<th>Hours after Dosage</th>
<th>Samples (n)</th>
<th>Isoniazid Dosage (mg/kg)</th>
<th>Concentration (mg/L)</th>
<th>Ratio CSF/Serum Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>19</td>
<td>8.5 ± 0.4</td>
<td>4.4 ± 0.5</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>9.1 ± 0.6</td>
<td>2.6 ± 0.8</td>
<td>3.2 ± 0.8</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>9.0 ± 0.8</td>
<td>2.1 ± 0.6</td>
<td>1.8 ± 0.5</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>7.5 ± 0.9</td>
<td>1.0 ± 0.3</td>
<td>1.8 ± 0.5</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Hours after Dosage</th>
<th>Samples (n)</th>
<th>Rifampin Dosage (mg/kg)</th>
<th>Concentration (mg/L)</th>
<th>Ratio CSF/Serum Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>19</td>
<td>10.7 ± 0.5</td>
<td>11.5 ± 1.0</td>
<td>0.39 ± 0.06</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>11.1 ± 0.5</td>
<td>10.6 ± 1.4</td>
<td>0.36 ± 0.06</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>10.1 ± 0.6</td>
<td>10.1 ± 1.1</td>
<td>0.78 ± 0.13</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>10.5 ± 0.8</td>
<td>4.7 ± 0.6</td>
<td>0.47 ± 0.06</td>
</tr>
</tbody>
</table>

Drug Penetration of CSF

Table 3: Anti-tuberculosis drugs used in TBM treatment (31–34,164).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral bio-availability (%)</th>
<th>Food effect</th>
<th>Plasma protein binding (%)</th>
<th>CNS penetration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>70</td>
<td>30%</td>
<td>89</td>
<td>10–20</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>80%</td>
<td>0–100</td>
<td>80–90</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>90%</td>
<td>None</td>
<td>90–100</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>75–80</td>
<td>None</td>
<td>20–30</td>
<td>20–30</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>50</td>
<td>Decreased rate of absorption</td>
<td>85</td>
<td>50</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>70</td>
<td>None</td>
<td>98</td>
<td></td>
</tr>
</tbody>
</table>


Table 4: Penetration of antituberculosis drugs into the CSF, their partition coefficients, plasma protein binding, renal excretion, and secretion in the saliva.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ethionamide</th>
<th>Prothionamide</th>
<th>Pyrazinamide</th>
<th>Isoniazid</th>
<th>Ethambutol</th>
<th>Streptomycin</th>
<th>Rifampicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penetration into the CSF</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+114*</td>
<td>+</td>
<td>+23**</td>
</tr>
<tr>
<td>Percentage ionized at body pH</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>166</td>
<td>188</td>
<td>123</td>
<td>137</td>
<td>204</td>
<td>562</td>
<td>823</td>
</tr>
<tr>
<td>Log P&lt;sub&gt;o&lt;/sub&gt; (partition coefficient)</td>
<td>1.05</td>
<td>1.88</td>
<td>-0.39</td>
<td>-1.17</td>
<td>ND&lt;sup&gt;9&lt;/sup&gt;</td>
<td>ND</td>
<td>1.93</td>
</tr>
<tr>
<td>Octanol/water</td>
<td>1.52</td>
<td>2.02</td>
<td>-0.46</td>
<td>-0.34</td>
<td>ND</td>
<td>ND</td>
<td>1.27</td>
</tr>
<tr>
<td>Cyclohexanol/water</td>
<td>-1.76</td>
<td>-1.28</td>
<td>-2.66</td>
<td>-2.54</td>
<td>ND</td>
<td>ND</td>
<td>-0.82</td>
</tr>
<tr>
<td>Log P&lt;sub&gt;o&lt;/sub&gt; - log P&lt;sub&gt;wa&lt;/sub&gt;</td>
<td>3.28</td>
<td>3.30</td>
<td>2.20</td>
<td>1.70</td>
<td>-</td>
<td>-</td>
<td>2.09</td>
</tr>
<tr>
<td>Plasma protein bound, (%)</td>
<td>30±**</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0–25±**</td>
<td>35±**</td>
<td>85</td>
</tr>
<tr>
<td>Apparent renal clearance rate, (m/min)</td>
<td>&lt;1&lt;sup&gt;9&lt;/sup&gt;</td>
<td>&lt;1&lt;sup&gt;9&lt;/sup&gt;</td>
<td>1.2&lt;sup&gt;9&lt;/sup&gt;</td>
<td>15&lt;sup&gt;9&lt;/sup&gt;</td>
<td>400–450&lt;sup&gt;9&lt;/sup&gt;</td>
<td>125</td>
<td>15&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Predicted CSF penetration relative to pyrazinamide&lt;sup&gt;±&lt;/sup&gt;</td>
<td>≫1††</td>
<td>≫1††</td>
<td>1</td>
<td>0.1</td>
<td>0.009</td>
<td>0.005</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Drug Penetration of CSF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral bioavailability (%)</th>
<th>Food effect</th>
<th>Plasma protein binding (%)</th>
<th>CNS penetration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td>PO; IV -100</td>
<td>None</td>
<td>24-38</td>
<td>70-80</td>
</tr>
<tr>
<td>Maxifloxacin</td>
<td>PO; IV 90</td>
<td>None</td>
<td>50</td>
<td>70-80</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>PO -100</td>
<td>None</td>
<td>-30</td>
<td>80-90</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>PO 65-90</td>
<td>Slight decrease</td>
<td>-0</td>
<td>80-90</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral bioavailability (%)</th>
<th>Food effect</th>
<th>Plasma protein binding (%)</th>
<th>CNS penetration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>PO; IV -100</td>
<td>-23% with high-fat meals</td>
<td>31</td>
<td>70</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>PO Unknown</td>
<td>Increase</td>
<td>&gt;99</td>
<td>Likely poor (limited data)</td>
</tr>
<tr>
<td>Delamanid</td>
<td>PO 25-47</td>
<td>Increase</td>
<td>&gt;99</td>
<td>No human data</td>
</tr>
<tr>
<td>Pretomanid</td>
<td>PO Unknown</td>
<td>Increase</td>
<td>93</td>
<td>No human data</td>
</tr>
</tbody>
</table>

Expert Review of Clinical Pharmacology, 12:3, 267-288

A Dose-Ranging Trial to Optimize the Dose of Rifampin in the Treatment of Tuberculosis

Martin J. Boeree1,2, Andreas H. Dacorn1,3, Rodney Dawson4, Kim Narunsky5,6, Jeannine du Bois1, Amour Venter1, Patrick P. J. Phillips1, Stephen H. Gillece1, Timothy D. McHugh7, Michael Hoelscher1,2,3, Norbert Heirich1,6, Sunita Rehal1, Dick van Sooijingen1,2,5, Jakko van Ingen1, Cécile Maples-Escoura1, David Burger1, Georgette Piempen van Balen1, and Rob E. Asmoutse1, on behalf of the PanACEA Consortium
Intensified Regimen for TBM

![Graph showing comparison between standard and intensified regimens for TBM treatment.](image)

- 15 mg/kg rifampin
- 20 mg/kg levofloxacin
- 10 mg/kg rifampin

11/26/2019

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Adjunctive Therapies

- Steroids decrease mortality without affecting morbidity

- Aspirin showed clear benefit in adult patients with TBM but had no effect on morbidity or mortality in children

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Journal of Child Neurology 2003(8) 956-962
Steroids

Figure 2. Kaplan-Meier curves by TBM grade. The blue solid lines correspond to the placebo group, the dashed red lines to the dexamethasone group.
doi:10.1371/journal.pone.0027821.g002

Steroids

A. All Patients

B. Patients Not Infected with HIV

C. Patients Infected with HIV


11/26/2019
Trip to Nepal

• At this point he planned a trip to Nepal

• He was instructed to:
  - Do monthly CBC and CMP, with results emailed to me
  - Do a monthly neuropathy check
  - Establish care with TB facility in Katmandu
  - Advised to seek Ophthalmology evaluation if any change in his baseline visual acuity

• Repeat MRI - no change
Back From Trip

- Felt well, weight increased from 112 lbs to 150 lbs
- 4 mg dexamethasone 2 tabs
- No adverse effects to therapy
- Isoniazid level - **0.8 mcg/ml** on 300mg
- Rifampin level - **1.05 mcg/ml** on 900mg

- If lab let the blood set on the counter instead of spinning down and freezing right away so drug did not decay???
6 months of Augmented ATT

Visual acuity issues:
- Difficulty reading fine print
- Held Linezolid for 2 weeks
- Visual acuity resulted 20/25 & color vision is 8/16 unchanged
- Optic disc was normal on Ophthalmology exam
- No improvement in visual acuity even with discontinuation of Linezolid
- Resumed Linezolid

Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis

- 58.9% of patients had adverse events (68.4% major)
  - Anemia 38.1%
  - Peripheral neuropathy 47.1%
  - GI disorders 16.7%
  - Optic neuritis 13.2%
  - Thrombocytopenia 11.8%

- 12 studies, 11 countries, 3 continents
- 121 patients
Where am I with my patient now?

- Difficulty with maintaining balance when he looks at something while walking
- No swaying or syncope or black outs or seizures
- MRI brain:
  - Stable appearance of the basilar meningitis pattern
  - Unchanged appearance of numerous small nodular and peripherally enhancing lesions both cerebral hemispheres in the right and left lobes of the cerebellum suggestive of small tuberculomas.
  - Stable pattern of vasogenic edema involving both cerebral hemispheres most pronounced in the right temporal lobe

Where am I with my patient now?

- Held linezolid
- Neurology evaluation
- Increased rifampin to 1250 mg
- Repeat levels in 2 weeks
- Lab informed to spin immediately
Thanks to
Thank You!