TB Case Conference Webinar

June 16th, 2016

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Special Thank You to Dr. John Wilson
Objectives

• Case Presentation
• Review epidemiology of MDR-TB meningitis in the United States
• Identify principles of infection control as it relates to MDR-TB
• Impact of drug resistance on the outcome of TB meningitis
• Palliative care for MDR TB?
Disclosures

• None
Case Presentation

- **Elderly Hmong male**, recent history of ischemic stroke and resultant left-sided hemiparesis- prolonged fevers and flu-like symptoms, treated for Influenza and HCAP

- Transferred to Mayo Clinic due to multiple new strokes, headache, weakness and **progressive somnolence and daily fever**

- PMHx: COPD, CHF due to ischemic cardiomyopathy (EF25%), atrial fibrillation, Chronic kidney disease, severe kyphoscoliosis

- **No prior TB history or treatment**
Social History

- Moved to the US from Laos in 1979, however made frequent trips back to Laos to visit friends and family
- Retired, was a farmer
- Independent prior to recent stroke
- Previous Nicotine use, no history of IVDU
- No known TB contacts
Physical exam

- T. max: 38.9, Spo2: 98% on 2 L NC, 156/78, HR 83 BPM
- General: Opens eyes to sternal rub
- Heart/Lung: irregular rate and rhythm; no murmurs, rubs, or gallops. Lungs: Breathing comfortably on 2L NC; Abdomen: Soft, non-distended; Skin: No rash
- MS: Unable to follow one step commands. Non-verbal.
- CRANIAL NERVES: Pupils equal in size and mildly reactive. No dysconjugate gaze. No facial droop. No ptosis. MOTOR SPEECH: Non-verbal during interview
- MUSCLE STRENGTH: Antigravity in the RUE, flaccid in LUE, flaccid in LLE, moves toes in RLE
- MUSCLE REFLEXES: Biceps 0/+1, Brachioradialis 0/+1, Quadriceps -1/+1, Gastroc-soleus -4/-4.
- SENSATION: Withdraws to pain in all 4 extremities.
Recent Medical History

- New fevers and cough
- Treated for influenza A

Living independently. No CNS deficits.

- Admitted to OSH with new left sided facial droop and weakness.
- MRI shows watershed infarcts in right MCA distribution
- New a.fib

- Transfered to SMH for further evaluation

December

Jan 1
- Admitted to OSH with new left sided facial droop and weakness.

Jan 11
- MRI shows watershed infarcts in right MCA distribution
- New a.fib

Jan 17
- HCAP rx: Vancomycin, levofoxacin, Piperacillin/Tazobactam
- Multiple BCx (-)

Jan 27
- Repeat MRI shows multifocal small acute and subacute right-sided infarcts
- Fluid in right mastoid air cells

- Discharged

- Readmitted to OSH for functional decline.

- Discharged

- TTE (-)

- EEG shows diffuse slowing, no seizure activity

- Discharged

- Repeat MRI shows multifocal small acute and subacute right-sided infarcts
- Fluid in right mastoid air cells
New multifocal restricted diffusion within the right cerebral hemisphere, most consistent with interval additional acute ischemic changes and likely contributing to clinical presentation. **Chronic-appearing lacunar infarcts** of right cerebral hemisphere and left thalamus.
Differential Diagnosis

70 year old Hmong male from Laos with febrile subacute encephalopathy in setting of recent CVA

- **Bacterial**
  - L. monocytogenes
  - TB
  - Culture-negative endocarditis
  - Syphilis
  - Neuro-brucellosis
  - S. pneumoniae (acute)
  - N. meningitidis (acute)

- **Fungal**
  - Histoplasma
  - Blastomyces
  - Coccidiomycosis
  - Cryptococcus

- **Viral**
  - HIV

- **Non-infectious**
  - CNS vasculitis
  - Paraneoplastic phenomenon
CXR, PA & Lateral
Case Unfolding

- Transferred to SMH for somnolence and fever
- ICU transfer for Airway protection
- CBC: Hb 11.9 WBC 7.1, Plt 258; Creatinine: 1.1, ALT 135 alk phos 116, AST 142, T.Bili: 0.9
- 1/27, 1/28 Blood Cx: NGTD
- QuantiFERON-TB: Positive at +9.9
- TEE: no vegetations
- Syphilis IgG Ab Positive, RPR Negative, Syphilis Ab by TP-PA, positive
- HIV screen Negative
LP Results

HD#2

- Glucose: <20
- Total Protein: 219
- TNC: 49
  - PMN: 64
  - Lymph: 28
- Opening pressure: not obtained
- VZV, HSV1/2, negative
- Gram stain, fungal smear
- TB: not performed
MC #1
Which of the following is true regarding TB epidemiology in Laos?

1. Incidence 20 cases per 100000
2. MDR rate of new cases 4.5 %
3. MDR among retreatment 50 %
4. Laos is TB Free
MC#2
What Empiric Regimen for possible TB meningitis would you recommend?

1. Isoniazid, rifampin, pyrazinamide, ethambutol + dexamethasone
2. Isoniazid, rifampin, pyrazinamide, moxifloxacin + dexamethasone
3. Ethionamide, Cycloserine, Moxifloxacin, Pyrazinamide, Amikacin + dexamethasone
4. Ethionamide, Cycloserine, Linezolid, Amikacin + dexamethasone
5. Something else
ID Consult, Empiric Regimen

- a) TB: moxifloxacin; rifampin; isoniazid; pyrazinamide
- (b) Antibacterial: ampicillin, vancomycin, cefepime → discontinued
- (c) Anti-fungal: fluconazole → discontinued
- (d) dexamethasone
- (e) Negative Pressure Airborne Isolation room
### Serial LPs

<table>
<thead>
<tr>
<th>HD#2</th>
<th>HD#4 (day 2 of rx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Glucose: &lt;20</td>
<td>- Glucose: 35</td>
</tr>
<tr>
<td>- Total Protein: 219</td>
<td>- Total Protein: 280</td>
</tr>
<tr>
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<td>- TNC: 45</td>
</tr>
<tr>
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<td>- PMN: 31</td>
</tr>
<tr>
<td>- Lymph: 28</td>
<td>- Lymph: 64</td>
</tr>
<tr>
<td>- Opening pressure: not obtained</td>
<td>- Opening pressure: 150</td>
</tr>
<tr>
<td>- VZV, HSV1/2, negative</td>
<td>- VDRL negative</td>
</tr>
<tr>
<td>- Gram stain, fungal smear</td>
<td>- Gram stain, fungal smear, AFB smear negative</td>
</tr>
<tr>
<td>- TB: not performed</td>
<td></td>
</tr>
</tbody>
</table>
MC #3 Is this CSF Profile consistent with TB meningitis?

1. Yes
2. No
3. I do not know
## Serial LPs

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<td>• TB: not performed</td>
<td>• MTB PCR: positive</td>
</tr>
</tbody>
</table>
Concern for INH Resistance by in-house Molecular Testing for KatGS315T
M. tuberculosis complex detection by PCR

- Laboratory-developed real-time PCR assay performed on the Roche LightCycler 2.0 instrument
- Target is the katG gene of M. tuberculosis complex
- A portion of the gene is amplified and detection is accomplished using sequence-specific FRET hybridization probes that sit over the katG S315T region; some information about INH resistance is obtained
- If the katG S315T mutation is detected, the report indicates “probable INH resistance detected”; confirmed with follow-up phenotypic testing after isolate grows in culture.
- If no katG S315T mutation is detected, Mayo lab will not comment on susceptibility since not all resistance determining genes are probed in the assay.
Real-time PCR Workflow for *M. tuberculosis* complex in our Laboratory

Approximate turn-around time = 4h

- Direct specimen or culture isolate lysis, inactivation and processing
- DNA extraction
- PCR amplification and detection

BSL 2+ (specimen) or BLS 3 (isolate) → BSL 2
Direct Detection of Mtb INH resistance using real-time PCR melt curve analysis

Temperature (°C)

Fluorescence
-d(F2/F1)/dT

S315T
WT
Why use a LDT PCR?

- closed PCR system – reduced opportunity for false-positives vs MTD assay
- used since 2008 (prior to FDA clearance of GeneXpert assay)
- can be used on a wider variety of specimen types including CSF and formalin-fixed, paraffin-embedded tissue blocks from pathology
- how does it compare to Cepheid GeneXpert MTB/RIF assay?

<table>
<thead>
<tr>
<th>All sources (smear + &amp; -)</th>
<th>Culture</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>27</td>
<td>2</td>
<td>84.4%</td>
<td>99.6%</td>
</tr>
<tr>
<td>Mayo LDT PCR</td>
<td>-</td>
<td>5</td>
<td>465</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>27</td>
<td>2</td>
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<td></td>
<td></td>
</tr>
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<td>Cepheid GeneXpert MTB/RIF</td>
<td>+</td>
<td>27</td>
<td>2</td>
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</tr>
<tr>
<td></td>
<td>-</td>
<td>5</td>
<td>465</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Change in Therapy

• Once INH resistance noted, combination tuberculosis therapy further modified:
  • Continued moxifloxacin, rifampin, pyrazinamide
  • Added ethambutol; IV amikacin
  • INH discontinued

• MDDR testing Pending from CDC
## Molecular Detection of Drug Resistance at CDC

<table>
<thead>
<tr>
<th>Locus (region) examined*</th>
<th>Result</th>
<th>Interpretation (based on in-house evaluation of 550 clinical isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rpoB (RRDR)</td>
<td>Mutation: TCG&gt;TGG; Ser531Leu</td>
<td>Rifampin resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are RMP-R.)</td>
</tr>
<tr>
<td>inhA (promoter)</td>
<td>No MTBC amplification detected**</td>
<td>Cannot rule out isoniazid resistance.</td>
</tr>
<tr>
<td>katG (Ser315 codon)</td>
<td>No MTBC amplification detected**</td>
<td>Cannot rule out ethambutol resistance.</td>
</tr>
<tr>
<td>embB (Met306,Gly406)</td>
<td>No MTBC amplification detected**</td>
<td>Cannot rule out PZA resistance.</td>
</tr>
<tr>
<td>pncA (promoter, coding region)</td>
<td>No MTBC amplification detected**</td>
<td>Cannot rule out fluoroquinolone resistance. (80% of FQR isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)</td>
</tr>
<tr>
<td>gyrA (QRDR)</td>
<td>No mutation</td>
<td>Cannot rule out resistance to injectable drugs (kanamycin, capreomycin, amikacin).</td>
</tr>
<tr>
<td>ms (1400 region)</td>
<td>No MTBC amplification detected**</td>
<td></td>
</tr>
<tr>
<td>els (promoter)</td>
<td>No MTBC amplification detected**</td>
<td></td>
</tr>
<tr>
<td>tlyA (entire ORF)</td>
<td>No MTBC amplification detected**</td>
<td></td>
</tr>
</tbody>
</table>

*A negative result (e.g., no mutation) does not rule out contributory mutations present elsewhere in the genome.

**The specimen did not contain *M. tuberculosis* complex (MTBC) organisms or did not contain sufficient numbers of MTBC organisms for successful amplification. These results should not be used to rule out the presence of MTBC in the sample.
Regimen?
Change in Therapy again

• Now due to finding of molecular evidence of INH and RIF resistance- new regimen:
  • Added linezolid at 600 mg daily
  • Added ethionamide, dose-escalating fashion
  • Stop Rifampin

• Updated 6 drug-Regimen:
  • Amikacin, Pyrazinamide, Ethambutol, linezolid, ethionamide, moxifloxacin
Serial LPs

HD#2
- Glucose: <20
- Total Protein: 219
- TNC: 49
  - PMN: 64
  - Lymph: 28
- Opening pressure: not obtained
- VZV, HSV1/2, negative
- Gram stain, fungal smear
- TB: not performed

HD#4 (day 2 of rx)
- Glucose: 35
- Total Protein: 280
- TNC: 45
  - PMN: 31
  - Lymph: 64
- Opening pressure: 150
- VDRL negative
- Gram stain, fungal smear, AFB smear negative
- MTB PCR: positive

HD#7 (day 5 of rx)
- Glucose: 62
- Total Protein: 134
- TNC: 29
  - PMN: 2
  - Lymph: 92
- Opening pressure: 135
- VDRL negative
- Gram stain, fungal smear AFB Smear negative
- MTB PCR: positive
Infection control - When to remove isolation?

• Sputum Samples unable to be completed
  • Induced sputum not successful

• Pt without pulmonary symptoms (prior to & during hospitalization)

• CT Chest- No focal airspace opacities

• Pulmonary Medicine - Bronchoscopy is too risky
  • (cardiomyopathy, kyphoscoliosis, asymptomatic)

• Pt has 3 Gastric Aspirate Washes done-negative for AFB *3
CT Chest
MC #4 Patient completed 4 weeks of therapy: When would you remove this patient from airborne isolation?

1. Not until completion of 2 months effective combination TB drug therapy irrespective of pulmonary vs. extrapulmonary disease

2. Now, because this is extrapulmonary TB disease & on effective therapy (no obvious findings for pulmonary disease – clinically or radiologically)

3. Not until CSF mycobacterial cultures have been confirmed negative

4. Never while in hospital or nursing home because of MDR status; drop isolation only if/when patient is going home

5. Never because respiratory samples could not be collected and tested for TB, despite clear CT scan and absence of pulmonary symptoms

6. Not until phenotypic DST results are available
Discussions within Infection Control:

• Infection Control concerns in MDR-TB cases
  • Abnormal CXR, possibly explained by overload and poor inspiratory effort
  • Negative CT chest for miliary or parenchymal disease
• No Pulmonary Symptoms
• Could not cough, cooperative with induced sputum
• Bronchoscopy deemed too risky
• Gastric wash x 3 negative AFB and MTB PCR
Infection Control

- Isolation was discontinued after 4 weeks of hospitalization (day +29)

- Gastric lavage/aspirate MTB PCR and stains and cultures remained negative to date
Are there formal guidelines?

- MDR TB, pulmonary or laryngeal- patients to remain in isolation pending sputum culture negativity

- MDR CNS with no radiological, clinical or microbiological evidence of Pulmonary TB?
<table>
<thead>
<tr>
<th>Serial LPs</th>
<th>HD#2</th>
<th>HD#4 (day 2 rx)</th>
<th>HD#7 (day 5 rx)</th>
<th>HD#34 (day 32 rx)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glucose: <strong>&lt;20</strong></td>
<td>Glucose: <strong>35</strong></td>
<td>Glucose: <strong>62</strong></td>
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</tr>
<tr>
<td></td>
<td>Total Protein: 219</td>
<td>Total Protein: 280</td>
<td>Total Protein: 134</td>
<td>Total Protein: 101</td>
</tr>
<tr>
<td></td>
<td>TNC: 49</td>
<td>TNC: 45</td>
<td>TNC: 29</td>
<td>TNC: 39</td>
</tr>
<tr>
<td></td>
<td>PMN: 64</td>
<td>PMN: 31</td>
<td>PMN: 2</td>
<td>PMN: 2</td>
</tr>
<tr>
<td></td>
<td>Lymph: 28</td>
<td>Lymph: 64</td>
<td>Lymph: 92</td>
<td>Lymph: 87</td>
</tr>
<tr>
<td></td>
<td>AFB smear negative</td>
<td>AFB Smear negative</td>
<td>AFB smear negative</td>
<td>MTB PCR: Negative</td>
</tr>
<tr>
<td></td>
<td>MTB PCR: positive</td>
<td>MTB PCR: positive</td>
<td>MTB PCR: positive</td>
<td>Culture Negative</td>
</tr>
<tr>
<td></td>
<td>Culture Positive</td>
<td>Culture Positive</td>
<td>Culture Positive</td>
<td></td>
</tr>
</tbody>
</table>
Pt Outcome

• Discharged on 3-15-16 from Mayo Clinic to a long term care facility

• Re-admitted to OSH with aspiration pneumonia, needing tracheostomy and PEG tube placement
Mycobacterium DST, in-house

3-FEB-2016 CEREBROSPINAL FLUID,
(Ordered 03-FEB-2016; Collected 03-FEB-2016 13:27; Received 03-FEB-2016 15:33) MCLab RO Main Campus
Fungal Smear only performed
ACID FAST Smeer FOR MYCOBACTERIUM
Negative.
FUNGAL Smeer
Negative. If a culture is desired, please contact Microbiology within 48 hours at Ext. 4-3625.
BACTERIAL CULTURE, AEROBIC + SUSC
No growth after 5 days of incubation.
GRAM STAIN
No organisms seen. White blood cells present.
MYCOBACTERIAL CULTURE
(Reported 03-FEB-2016 21:48) FINAL
(Reported 03-FEB-2016 18:19) FINAL
(Reported 08-FEB-2016 10:13) FINAL
(Reported 03-FEB-2016 16:15) FINAL
(Reported 04-APR-2016 15:15) FINAL

MYCOBACTERIUM TUBERCULOSIS COMPLEX
Infectious Diseases consult recommended. Reportable Disease. Infection Prevention and Control will report to the Minnesota Department of Health, when applicable.
Previous comment was modified at 15:15 on 04/04/2016: Infectious Diseases consult recommended.
Reportable Disease. Infection Prevention and Control will report to the Minnesota Department of Health, when applicable. Confirmation testing pending.
First line agents tested by broth dilution using critical concentrations and CLSI interpretive criteria. Second line agents tested by microbroth dilution with the MIC reported and using laboratory developed interpretive criteria.
Previous comment was modified at 15:15 on 04/04/2016: First line agents tested by broth dilution using critical concentrations and CLSI interpretive criteria.
S=Susceptible; I=Intermediate; R=Resistant; N=Not susceptible; D=Susceptible dose-dependent;
Results in mcg/mL

MYCOBACTERIUM TUBERCULOSIS COMPLEX
Ethambutol 5 R Ethambutol 8 R Isoniazid 0.1 R
Isoniazid 0.4 R Pyrazinamide 300 S Rifampin 1.0 R
Amikacin <=0.12 S Ethionamide 1.2 S Kanamycin <=0.6 S
Moxifloxacin 0.25 S p-Aminosalicylic acid <=0.5 S
Rifabutin 4 R Streptomycin >32 R
Ethambutol 5: Resistance confirmed by second method.
Isoniazid 0.1: Resistance confirmed by second method.
Rifampin 1.0: Resistance confirmed by second method.
# CDC Susceptibility Testing

**Susceptibility Testing Method: Indirect agar proportion, 7H10 medium; Susceptibility is defined as < 1% resistance compared to colonies that develop on drug-free media.**

**RESULTS:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent Resistance</th>
<th>Interpretation</th>
<th>Drug</th>
<th>Percent Resistance</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid 0.2 ug/ml</td>
<td>100</td>
<td>R</td>
<td>Kanamycin 5.0 ug/ml</td>
<td>0</td>
<td>S</td>
</tr>
<tr>
<td>Isoniazid 1.0 ug/ml</td>
<td>100</td>
<td>R</td>
<td>Ethionamide 10.0 ug/ml</td>
<td>0</td>
<td>S</td>
</tr>
<tr>
<td>Isoniazid 5.0 ug/ml</td>
<td>100</td>
<td>R</td>
<td>Capreomycin 10.0 ug/ml</td>
<td>0</td>
<td>S</td>
</tr>
<tr>
<td>Rifampin 1.0 ug/ml</td>
<td>100</td>
<td>R</td>
<td>PAS 2.0 ug/ml</td>
<td>0</td>
<td>S</td>
</tr>
<tr>
<td>Ethambutol 5.0 ug/ml</td>
<td>100</td>
<td>R</td>
<td>Ofloxacin 2.0 ug/ml</td>
<td>0</td>
<td>S</td>
</tr>
<tr>
<td>Streptomycin 2.0 ug/ml</td>
<td>100</td>
<td>R</td>
<td>Amikacin 4.0 ug/ml</td>
<td>0</td>
<td>S</td>
</tr>
<tr>
<td>Streptomycin 10.0 ug/ml</td>
<td>100</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin 2.0 ug/ml</td>
<td>see comments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin 2.0 ug/ml</td>
<td>0</td>
<td>S</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Susceptibility Testing Method: MGIT 960**

**Pyrazinamide 100 ug/ml**: Susceptible

**Comments:**

Molecular Detection of Drug Resistance (MDDR) report was issued 4/29/2016.

These conventional agar proportion results agree with the MDDR results.

**EXCEPTION:** Based on the Ser531Leu mutation detected in rpoB in the MDDR analysis, this isolate is resistant to rifabutin. This conflicts with the result obtained by agar proportion testing (rifabutin-S).

MIC testing for DDQ, CFZ, and LJ is in progress.
Patient Course

• During OSH hospitalization, due to thrombocytopenia, linezolid was held, cycloserine added

• Ethambutol discontinued based on Susceptibilities

• 5-Drug Regimen: Ethionamide, Cycloserine, Moxifloxacin, Pyrazinamide, Amikacin

• Continued to be managed through local health department
MDR TB in CNS disease

True Prevalence/Incidence is unknown
- USA 1993-2005-1,649 CNS TB cases
  234 patients (14%) were resistant to at least 1 first-line.
  133 of 1,649 (8%) patients were infected with an isolate resistant to at least isoniazid.
  24 patients meet MDR-TB criteria
- USA, 2014- 9421 TB cases
  96 were MDR TB (1.4% ); 88% foreign born

Globally MDR TB  3.5% of the 9 million cases in 2013

CNS TB can occur in 15-20% of TB cases in endemic regions
- In low endemic regions (US), can account for 1-5% of extra-pulmonary TB

Laos:
• Incidence 189 cases per 100,000
• MDR rate of new cases 4.5%
• MDR among retreatment 23%
CNS presentation of TB disease

- Meningitis
- Parenchymal TB: tuberculomas (most common), abscess, cerebritis
- TB cerebrovascular disease
TB cerebrovascular disease

• Stroke in TBM is common
  13-35% have CT-proven stroke
  Up to 57% have MRI evidence of stroke
  22-56% have autopsy-proven cerebral infarctions

• Stroke in TB meningitis Increases the odds of death
  TBM in with infarcts  x 3 risk of death
  In survivors, the extent of vascular damage predict functional outcome

• Stroke might be related to the stage of TBM
  In the univariant analysis along with HTN, Hydrocephalus

Pathophysiology of TB cerebrovascular diseases

• Vasculopathy
  - Arteritis (infiltrative, proliferative, necrotizing)
  - Thrombosis
  - Aneurysmal changes

• Hypercoagulable status (systemically)

• Cytokine mediated endothelial damage

Impact of resistance on outcome

- 180 patients, Vietnam

- 40% showed resistance to at least one agent

- 5% MDR

- MDR had RR of death 11.63

198 HIV patients with TB meningitis, enrolled in clinical trials

## Impact on mortality II

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid resistance</td>
<td>2.07 (1.30 to 3.29)</td>
<td>0.002</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.20 (0.88 to 1.63)</td>
<td>0.243</td>
</tr>
<tr>
<td>Age categories (years):</td>
<td>Overall &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>0.076 (0.008 to 0.69)</td>
<td>0.022</td>
</tr>
<tr>
<td>&gt;1 to ≤4</td>
<td>0.23 (0.067 to 0.82)</td>
<td>0.023</td>
</tr>
<tr>
<td>&gt;4 to ≤14</td>
<td>0.38 (0.102 to 1.41)</td>
<td>0.144</td>
</tr>
<tr>
<td>&gt;14 to ≤24</td>
<td>1.22 (0.64 to 2.34)</td>
<td>0.540</td>
</tr>
<tr>
<td>&gt;24 to ≤34</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>&gt;34 to ≤44</td>
<td>1.30 (0.87 to 1.92)</td>
<td>0.197</td>
</tr>
<tr>
<td>&gt;44 to ≤54</td>
<td>1.97 (1.23 to 3.15)</td>
<td>0.005</td>
</tr>
<tr>
<td>&gt;54 to ≤64</td>
<td>1.83 (1.09 to 3.09)</td>
<td>0.023</td>
</tr>
<tr>
<td>&gt;64 to ≤74</td>
<td>4.36 (2.48 to 7.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;74</td>
<td>6.90 (3.85 to 12.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race categories:</td>
<td>Overall &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>1.44 (1.01 to 2.06)</td>
<td>0.046</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.21 (0.74 to 1.99)</td>
<td>0.431</td>
</tr>
<tr>
<td>Asian*, non-Hispanic</td>
<td>0.64 (0.30 to 1.35)</td>
<td>0.220</td>
</tr>
<tr>
<td>American Indian, non-Hispanic</td>
<td>9.07 (2.65 to 31.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other†, non-Hispanic</td>
<td>0.85 (0.20 to 3.52)</td>
<td>0.819</td>
</tr>
<tr>
<td>HIV positive</td>
<td>3.57 (1.87 to 6.82)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**USA 1993-2005**

1896 CNS TB cases

What can we do?

- Suspect resistance
- Earlier diagnosis of resistance
  - Role of DST directly from patient specimens
- Earlier initiation of effective program
  - 5 active agents
    - Active first line agent
    - Fluoroquinolone
    - Injectable agent
    - Other second line active agents
      - With the best CNS penetration and least toxic
- DOT
- TDM
- Manage and anticipate drug toxicity
- Adjunctive steroids for the meningitis
## Creating a regimen

<table>
<thead>
<tr>
<th>Actions needed</th>
<th>Drug to consider</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong> Choose an injectable (group 2) drug based on drug-susceptibility testing and treatment history</td>
<td>Kanamycin; amikacin; capreomycin</td>
<td>Streptomycin is generally not used because of high rates of resistance in patients with MDR disease</td>
</tr>
<tr>
<td><strong>Step 2</strong> Choose a higher generation of fluoroquinolone (group 3)</td>
<td>Levofloxacin; moxifloxacin</td>
<td>If levofloxacin (or ofloxacin) resistance is documented, use moxifloxacin; avoid moxifloxacin if possible when using bedaquiline</td>
</tr>
<tr>
<td><strong>Step 3</strong> Add two or more group 4 drugs until there are at least four second-line antituberculosis drugs likely to be effective</td>
<td>Cycloserine/terizidone; para-aminosalicylic acid; ethionamide/protionamide</td>
<td>Ethionamide and protionamide are considered the most effective group 4 drugs; consider treatment history side-effect profile and cost; drug-susceptibility testing is not considered reliable for the drugs in this group</td>
</tr>
<tr>
<td><strong>Step 4</strong> Add group 1 drugs</td>
<td>Pyrazinamide; ethambutol</td>
<td>Pyrazinamide is routinely added in most regimens; ethambutol can be added if the criteria for an effective drug are met*; if susceptibility to isoniazid is unknown or pending it can be added to the regimen until drug-susceptibility testing results become available</td>
</tr>
<tr>
<td><strong>Step 5</strong> Consider adding group 5 drugs if four second-line antituberculosis drugs are not likely to be effective from groups 2–4</td>
<td>Bedaquiline; linezolid; clofazimine; amoxicillin/clavulanate; imipenem and cilastatin plus clavulanate; meropenem plus clavulanate; high-dose isoniazid; clarithromycin; thioacetazone</td>
<td>If drugs are needed from this group, two or more should be added; drug-susceptibility testing is not standardised for the drugs in this group</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Description</th>
<th>Estimated Ratio of CSF to Plasma Concentration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>300 mg</td>
<td>80–90%</td>
<td>Essential drug; good CSF penetration throughout treatment</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>450 mg (weight &lt;50 kg) or 600 mg (weight ≥50 kg)</td>
<td>10–20%</td>
<td>Essential drug, despite relatively poor CSF penetration; higher doses might improve effectiveness</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1.5 g (weight &lt;50 kg) or 2.0 g (weight ≥50 kg)</td>
<td>90–100%</td>
<td>Excellent CSF penetration throughout treatment</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg/kg</td>
<td>20–30%</td>
<td>Poor CSF penetration once meningeval inflammation resolves</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15 mg/kg (1 g maximum)</td>
<td>10–20%</td>
<td>Poor CSF penetration once meningeval inflammation resolves</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>15 mg/kg</td>
<td>10–20%</td>
<td>Poor CSF penetration once meningeval inflammation resolves</td>
</tr>
<tr>
<td>Amikacin</td>
<td>15–20 mg/kg</td>
<td>10–20%</td>
<td>Poor CSF penetration once meningeval inflammation resolves</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>70–80%</td>
<td>Good CSF penetration</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1000 mg</td>
<td>70–80%</td>
<td>Good CSF penetration</td>
</tr>
<tr>
<td>p-Aminosalicylic acid</td>
<td>10–12 g</td>
<td>No data</td>
<td>Probably very poor CSF penetration unless meninges are inflamed</td>
</tr>
<tr>
<td>Ethionamide or prothionamide</td>
<td>15–20 mg/kg (1 g maximum)</td>
<td>80–90%</td>
<td>Good CSF penetration</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>10–15 mg/kg</td>
<td>80–90%</td>
<td>Good CSF penetration</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1200 mg</td>
<td>40–70%</td>
<td>Variable interindividual CSF pharmacokinetics</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15–20 mg/kg</td>
<td>No data</td>
<td>..</td>
</tr>
</tbody>
</table>

Table 4: CSF penetration of first-line and second-line antituberculosis drugs

How many active agents?

Aggressive regimens in management of MDR TB

- Aggressive regimen decreases mortality
  - 669 patients were treated for laboratory-confirmed MDR-TB*
  - Those who received aggressive regimen had HR of 0.62 for death
  - Aggressive regimen =
    - At least 5 agents (FQ + injectable) for 6 months after culture conversion
    - Followed by 4 active oral agents for continuation phase

- Aggressive regimen decrease recurrences
  - 402 MDR TB patients
  - Those who received aggressive regimen had a HR of 0.4 for recurrence
  - 5 active agents (FQ + Injectable) for 18 months following culture conversion

Controversies in MDR TB

• Question of Palliative care in MDR-TB cases
  • Manage patient's symptoms, avoid adverse effects of drugs, but protect family members and healthcare workers with ongoing exposure to patient, societal implication of untreated MDR-TB
New Directions

• Improving molecular diagnostics
• Host directed therapies, beyond steroids
• Repurposed medications
• Newer anti-TB agents
Questions and Discussion