XDR TB:
The Laboratory’s Dilemma
vs
The Clinician’s Dilemma

Barbara J. Seaworth, MD, FIDSA, FACP, Heartland National TB Center, San Antonio, TX

Kenneth Jost, Jr., M(ASCP) Laboratory Services Section, Texas Department of State Health Services
Only ~7% of MDR is diagnosed with DST

Only ~16% MDR is treated according to WHO standards.
Dangerous TB Patient Detained on U.S. Mexico Border

In medical isolation in South Texas, 100 miles or so from Mexico's border, is a man who embodies one of U.S. health officials' greatest worries: He is the first person to cross and be held in detention while infected with one of the most severe types of drug-resistant tuberculosis known today. His three-month odyssey through 13 countries—from his homeland of Nepal through South Asia, Brazil, Mexico, and finally into Texas—shows the way in which dangerous new strains of the disease can migrate across the world unchecked.

WSJ March 1, 2013
Potential Global Exposure

1. India
2. Dubai
3. Brazil
4. Bolivia
5. Peru
6. Ecuador
7. Columbia
8. Panama
9. Costa Rica
10. Nicaragua
11. El Salvador
12. Guatemala
13. Mexico

United States
Multiple Exposures Over Hundreds of Miles

- Airplane flight > 12 hours
- Traveled by car across several countries in South and Central America
- Detained for > 1 week in a cell in Panama
- 48 hours in a safe house with > 30 people (2 rooms, no windows) in Reynosa
- 3 Days in Border Patrol Custody in a crowded cell
Case Study

• 24 year old Asian male - ICE custody 12/1/2012
  – Abnormal CXR bilateral disease consistent with TB
  – TST + 13mm

• Placed in isolation within three hours of arrival

• INH, rifampin, ethambutol and PZA treatment initiated 12/5/2012

• Denies history of prior TB or exposure to persons with TB or chronic cough
Initial Assessment

• Patient noted cough and back pain
  • Several episodes of blood streaked sputum

• Wheezing on exam

• No other medical problems
  – Laboratory assessment normal
  – HIV negative - Hepatitis panel negative
Sputum Specimen Results December 2012

12/1  Sputum Collected
12/3  Received specimen
12/4  4+ smear positive
12/12 Mtb culture positive
12/17 MGIT DST
## Initial Drug Susceptibility Tests

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lab A MGIT</th>
<th>Austin GeneXpert</th>
<th>CDC MDDR</th>
<th>Lab A 7H10</th>
<th>Austin 7H10</th>
<th>CDC 7H10</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH High Conc.</td>
<td>R</td>
<td></td>
<td>unknown mutation</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>RMP</td>
<td>R</td>
<td>R (Probe E)</td>
<td>R (Ser531Leu)</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>EMB</td>
<td>R/S</td>
<td></td>
<td>Probably R (Met306Ile)</td>
<td>S</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>PZA</td>
<td>R</td>
<td></td>
<td>unknown mutation</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>OFL</td>
<td></td>
<td>R (Asp94Ala)</td>
<td></td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>KAN</td>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>AMK</td>
<td></td>
<td></td>
<td>R (A1401G)</td>
<td></td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>CAP</td>
<td></td>
<td></td>
<td></td>
<td>S</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>RBT</td>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>ETH</td>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

| Days post collection | 16 | 19 | 25 | 30 | 47 | 55 |
Additional Drug Susceptibility Tests
Some Good News

• Linezolid  S  Day 36
• Cycloserine  S  Day 53
• PAS  S  Day 53
• Clofazimine  S  Day 58
PAS Drug Susceptibility Test Results

- Day 53, Lab 1, 7H11 (8 mcg/ml), Susceptible (0%R)
- Day 55, Lab 2, 7H10 (2mcg/ml), Resistant (100%R)
## WHO Drug Susceptibility Test Methodology and Critical Concentrations

**Table 2. Current status of DST methodology and critical concentrations for second-line DST**

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Drug</th>
<th>DST category</th>
<th>DST method available</th>
<th>DST critical concentrations (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Löwenstein-Jensen³</td>
<td>Middlebrook 7H10³</td>
</tr>
<tr>
<td>Group 1</td>
<td>Isoniazid</td>
<td>I</td>
<td>Solid, liquid</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td>I</td>
<td>Solid, liquid</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td>II</td>
<td>Solid, liquid</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>II</td>
<td>Liquid</td>
<td>-</td>
</tr>
<tr>
<td>Group 2</td>
<td>Streptomycin</td>
<td>II</td>
<td>Solid, liquid</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Kanamycin</td>
<td>II</td>
<td>Solid, liquid</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>II</td>
<td>Liquid</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
<td>II</td>
<td>Solid, liquid</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>Viomycin</td>
<td>V</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Group 3</td>
<td>Ciprofloxacin</td>
<td>III</td>
<td>Solid, liquid</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Ofloxacin</td>
<td>III</td>
<td>Solid, liquid</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>IV</td>
<td>Solid, liquid</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>IV</td>
<td>Liquid</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Gatifloxacin</td>
<td>IV</td>
<td>Solid</td>
<td>-</td>
</tr>
<tr>
<td>Group 4</td>
<td>Ethionamide</td>
<td>IV</td>
<td>Solid, liquid</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>Prothionamide</td>
<td>IV</td>
<td>Solid, liquid</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>Cycloserine</td>
<td>IV</td>
<td>Solid, liquid</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>IV</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td><strong>β-amino-salicylic acid</strong></td>
<td>IV</td>
<td>Solid, liquid</td>
<td>1.0</td>
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<tr>
<td>Group 5</td>
<td>Clofazimine</td>
<td>V</td>
<td>Liquid</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin/clavulanate</td>
<td>V</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>V</td>
<td>Liquid</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>V</td>
<td>Liquid</td>
<td>-</td>
</tr>
</tbody>
</table>

1. WHO Guidelines for the programmatic management of drug-resistant tuberculosis (5).
2. Indirect proportion method recommended. Other solid media methods (resistance ratio, absolute concentration) have not been adequately validated for second-line drugs.
3. Routine DST for group 4 and 5 drugs is not recommended.
4. Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB (5).
5. Gatifloxacin only to be used in exceptional circumstances (5).
**PAS Agar MIC Follow-up Test Results**

<table>
<thead>
<tr>
<th>PAS (mcg/ml)</th>
<th>% Resistance</th>
<th>7H10</th>
<th>7H11</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>50%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>25%</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>8</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

- Categorical equivalence
- But are equivalent critical concentrations actually equivalent?
## Moxifloxacin MIC Distribution for Isolates with gyrA GAC>GCC; Asp94Ala

<table>
<thead>
<tr>
<th>Mox MIC (mcg/ml)</th>
<th># of isolates:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study 1</td>
</tr>
<tr>
<td></td>
<td>MGIT</td>
</tr>
<tr>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Asp94Ala associated with moderate FQ resistance

Study 1 Lin G, Desmond E, Schecter G, Jost K, Ortiz, E. 2010 ASM General Meeting
Study 3 CDC unpublished data
# Fluoroquinolone MICs

<table>
<thead>
<tr>
<th>Lab</th>
<th>Method</th>
<th>Ofloxacin</th>
<th>Levofloxacin</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MIC</td>
<td>Interp.</td>
<td>MIC</td>
</tr>
<tr>
<td>A</td>
<td>Sensititre</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>BACTEC 460</td>
<td>4</td>
<td>MS</td>
<td>2.0</td>
</tr>
<tr>
<td>C</td>
<td>MIGT 960</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>7H10 AP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>7H10 AP (repeat)</td>
<td>2.0</td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>D</td>
<td>Sensititre</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Subsequent patient isolate moxifloxacin MIC = 1.0 reported as Resistant

** No MIC interpretation but MGIT critical conc. 0.25mcg/ml reported as Resistant
Best Approach?

• 12/18/2012 laboratory reports resistance to INH and rifampin
  – Treatment held

• CXR (#2) 12/18/2012
  – “Increasing bilateral densities”

• CXR (#3) 12/28/2012
  – Increasing opacities compared to 12/18”

Do No Harm
When Should I Start Empiric Treatment for MDR TB?

- If patient is stable and they can be separated from high risk contacts in the home, it is best to wait until molecular tests and/or 2\textsuperscript{nd} line susceptibility tests available.
  - Avoid surprises
  - Avoid amplification of drug resistance

- If patient is unstable, start treatment while waiting for molecular and standard test results. Most experts would start with 6 or more drugs and then withdraw extra drugs later
When Can We Start Therapy?

WHO and CDC Guidelines Recommend at least 4 drugs to which isolate is likely to be susceptible

Not Yet!!
Susceptibility Studies

• Susceptible
  – Linezolid ≤ 4.0 mcg/ml
  – Cycloserine
  – Clofazimine < 0.06 mcg/ml
  – Moxifloxacin ≤ 1.0 mcg/ml

4 drugs Does Moxi Count?
Treatment Course

• Treatment started 2/22/2014 with:
  – Moxifloxacin
  – Linezolid
  – Cycloserine
  – Clofazimine
  – (Vitamin B 6)

• TMC207 anticipated within 2 weeks

• Back pain and hemoptysis resolve; Cough better
Bacteriological Response to Treatment

- AFB >10
- MGIT >10
- Agar +
- INH
- Rifampin
- PZA
- EMB

Colony counts and time to MGIT culture positive in days:
- Time Since Initial Diagnosis (weeks):
  - Rx Day 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33
  - Time to MGIT Culture Positive (Days):
    - (5) (5) (5)
    - (21) (27)
    - (23) (27)
    - (23) (20)
    - TMC 207 (Day 64)

Moxifloxacin, Cycloserine, Clofazimine, Linezolid

Indicates negative culture

1st Negative

(+) Indicates positive culture
Environmental Assessments at Border Patrol Stations

- Cell capacities between 45–100 detainees
- 0–3 air changes per hour (ACH) in cells
- 6 –9 ACH in isolation rooms
  - >12 ACH is recommended for buildings constructed after 2001*
- Pressure differential meters not functioning properly in one station
  - *CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in healthcare settings, 2005. MMWR 2005(54)R-17:1–
Conclusions

- **Did transmission occur?**
  - No secondary TB cases have been identified
  - No known test conversions among BP or ICE staff
  - Detainee TST conversions may not indicate recent transmission

- **Only one other case with matching genotype in a person born in the same country as the index patient**

- **Collaboration among all partners is critical to the success of multi-jurisdictional TB contact investigations**
What About The Contacts Who Convert?

• Very few converters noted but most close contacts were not identified.

• Will moxifloxacin have any effect on LTBI?

Can labs and clinicians evaluate various DST systems and better identify critical cut points/MICs that correlate with clinical outcomes?
gyrA Mutation & FQ MIC Distribution
You can’t prevent TB with a fence.