Drug Resistant TB within International Under-resourced Settings

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Mayo Clinic
Patient History

- 29 year old male from Hinche, Haiti
- 2012-2013 – exchange student in Ohio studying agriculture
- Tetralogy of Fallot recognized -- referred for surgical correction at the Cleveland Clinic
  - Sponsored by church group
- Preoperative assessment May 2013
  - Accepted as charitable case by CCF Pediatric Cardiology
- Returned to Haiti from May until August 2013
  - Typhoid fever
- Returned to CC in August 2013 for surgery
  - *Patient found to have fever, cough, and weight loss during previous 2 months in Haiti
Past medical history

• Tetralogy of Fallot
  – Hypoplastic left lung – chronic/long standing

• Pleural effusion at least since 2009
  – reportedly negative TB evaluation with thoracentesis in Haiti

• HIV negative
August 2013 Cleveland Clinic

• Pre-operative assessment in Thoracic Surgery
  – CXR
  – CT chest obtained for surgical planning
    • Cavitary right sided lesions
    • Left brochopleural fistula

• Sent to ER for TB evaluation
  – Airborne precautions initiated
  – AFB x 3 requested
  – Pleural fluid obtained
Chest XR August 2013
Patient admitted to hospital
Resp. Isolation / Neg. pressure room

• 8/23/13 Sputum
  – AFB smear (+), many
  – MTB PCR (+)
  – Later: (+) MTB culture growth

• 8/23/12 Pleural fluid – as much fluid as possible aspirated
  – AFB smear (-) neg.
  – Later: Culture (+) MTB
Timeline of Events

• AFB smear (+) sample sent to CDC via Ohio Dept. Health for DST and molecular diagnostics

• 8/30/2013: Initial regimen started
  – INH, Rifampin, PZA, Ethambutol
Question #1

How does TB incidence (per 100,000 population) in Haiti compare to other countries in the Western Hemisphere?

- Countries in North America, Caribbean, Central America, South America

1. First
2. Second
3. Fifth
4. Tenth
5. TB never seen in Haiti
TB in Haiti – 2012
WHO Data

• TB incidence ~ 22,000 cases
  – 213 (176-254) per 100k population
  – 20% TB patients are HIV (+) infected

• TB Prevalence: 296 (140-509) per 100k

• MDR TB estimates (in Haiti – 2012)
  – New TB cases ~2.2% (approx 400 pts)
  – Retreatment ~14%
PAHO – Regional TB report, 2011

Figure 5. Estimated TB incidence in the Region of the Americas, 2010

Figure 6. Region of the Americas: Top 10 countries by estimated TB incidence (Per 100,000 population)

Box 1. Region of the Americas: Top 10 countries by estimated numbers of incident TB cases (Highlighted in red: >80% of the regional burden)

<table>
<thead>
<tr>
<th>N.</th>
<th>Country</th>
<th>Incident TB cases</th>
<th>%</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Brazil</td>
<td>85,000</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>2</td>
<td>Peru</td>
<td>31,000</td>
<td>12%</td>
<td>43%</td>
</tr>
<tr>
<td>3</td>
<td>Haiti</td>
<td>23,000</td>
<td>8.6%</td>
<td>52%</td>
</tr>
<tr>
<td>4</td>
<td>Mexico</td>
<td>18,000</td>
<td>6.7%</td>
<td>59%</td>
</tr>
<tr>
<td>5</td>
<td>Colombia</td>
<td>16,000</td>
<td>6.0%</td>
<td>65%</td>
</tr>
<tr>
<td>6</td>
<td>Bolivia (Plurinational State of)</td>
<td>13,000</td>
<td>4.9%</td>
<td>70%</td>
</tr>
<tr>
<td>7</td>
<td>United States</td>
<td>13,000</td>
<td>4.9%</td>
<td>75%</td>
</tr>
<tr>
<td>8</td>
<td>Argentina</td>
<td>11,000</td>
<td>4.1%</td>
<td>79%</td>
</tr>
<tr>
<td>9</td>
<td>Venezuela</td>
<td>9,700</td>
<td>3.6%</td>
<td>82%</td>
</tr>
<tr>
<td>10</td>
<td>Ecuador</td>
<td>9,400</td>
<td>3.5%</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>37,880</td>
<td>14%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Tuberculosis in the Region of the Americas
Question #2

Management approach in this patient with pulmonary and pleural TB with suspected bronchopleural fistula:

1. Medical management alone, guided by DST
2. Chest tube insertion
3. Immediate surgical resection of BPF and possible decortication of hypoplastic left lung
4. Delay surgical resection after a few months of effective antimicrobial therapy
5. Consider pleural window creation
6. Other approach
Timeline of Events

- **8/30/2013**: Molecular diagnostic gene mutation testing
  - INH & rifampin resistance detected (report)
    - Moxifloxacin and amikacin added

- Early September additional drug resistance detected by MDDR
  - Antimicrobial therapy temporarily held
MDDR testing by CDC

**Results for Molecular Detection of Drug Resistance (Sanger Sequencing, complete panel, katG by pyrosequencing); Conventional Drug Susceptibility Test in progress.**

<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>1 (RRDR)</td>
<td>Mutation: TCG-&gt;TTG; 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>Mutation: T-8C</td>
<td>Isotiazidd resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are INH-R.)</td>
</tr>
<tr>
<td>katG (ser316 codon)</td>
<td>Mutation: AGC-&gt;ACC; Ser315Thr</td>
<td></td>
</tr>
<tr>
<td>embB (Met1306,Gly406)</td>
<td>Mutation: GCC-&gt;GCA; Gly406Ala</td>
<td>Ethambutol resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are EMB-R.)</td>
</tr>
<tr>
<td>pncA (promoter, coding region)</td>
<td>Unable to interpret data; No result</td>
<td>Cannot rule out FZA resistance.</td>
</tr>
<tr>
<td>gyrA (QRDR)</td>
<td>No mutation</td>
<td>Cannot rule out fluoroquinolone resistance. (80% of FQ-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)</td>
</tr>
<tr>
<td>ms (1400 region)</td>
<td>Mutation: C1459T</td>
<td>The effect of the ms C1459 mutation on drug resistance is unknown. Cannot rule out resistance to injectable drugs (kanamycin, capreomycin, amikacin). (In our in-house evaluation of 550 clinical isolates:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 91% of AMK-R isolates have a different mutation in the ms locus;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 87% of KAN-R isolates have a different mutation in the ms locus or a mutation in the els locus;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 55% of CAP-R isolates have a different mutation in the ms locus or a mutation in the tlyA locus.)</td>
</tr>
<tr>
<td>els (promoter)</td>
<td>No mutation</td>
<td></td>
</tr>
<tr>
<td>tlyA (entire ORF)</td>
<td>Unable to interpret data; No result</td>
<td></td>
</tr>
<tr>
<td>rpoB (RRDR)</td>
<td>Mutation: TCG-&gt;TTG; 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>
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**Results for Molecular Detection of Drug Resistance (Sanger Sequencing, complete panel, kaffi by pyrosequencing; Conventional Drug Susceptibility Test in progress.**

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<tr>
<td>InhA (promoter)</td>
<td>Mutation: T-8C</td>
<td>Isoniazid resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are INH-R.)</td>
</tr>
<tr>
<td>ketG (ser315 codon)</td>
<td>Mutation:** AGC(\rightarrow)ACC; Ser315Thr</td>
<td>Ethambutol resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are EMB-R.)</td>
</tr>
<tr>
<td>pncA (promoter, coding region)</td>
<td>Unable to interpret data; No result</td>
<td></td>
</tr>
<tr>
<td>gyrA (QRDR)</td>
<td>No mutation</td>
<td>Cannot rule out fluoroquinolone resistance. (80% of FQ-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)</td>
</tr>
<tr>
<td>rs (1400 region)</td>
<td>Mutation: C1499T</td>
<td>The effect of the rs C1499 mutation on drug resistance is unknown. Cannot rule out resistance to injectable drugs (kanamycin, capreomycin, amikacin). (In our in-house evaluation of 550 clinical isolates: 91% of AMK-R isolates have a different mutation in the rs locus; 87% of KAN-R isolates have a different mutation in the rs locus or a mutation in the els locus; 55% of CAP-R isolates have a different mutation in the rs locus or a mutation in the tlyA locus.)</td>
</tr>
<tr>
<td>els (promoter)</td>
<td>No mutation</td>
<td></td>
</tr>
<tr>
<td>tlyA (entire ORF)</td>
<td>Unable to interpret data; No result</td>
<td></td>
</tr>
<tr>
<td>rpoB (RRDR)</td>
<td>Mutation: TCG(\rightarrow)TTG; 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>
</tbody>
</table>
Timeline of Events

• 9/12/2013: New regimen initiated (in discussion with ODH & CDC)
  – Cycloserine 250mg bid
  – Ethionamide 750mg daily
  – Moxifloxacin 400mg daily
  – Amikacin 600mg daily
  – PZA 1000mg daily

• Phenotypic DST results *pending* (CDC & NJMC)
10/6/2013- M1 LMCA region stroke hemiparesis, aphasia

- tPA administered; transferred to ICU
- CT brain– left MCA stroke, cavitary brain lesion
- CSF negative culture, no WBCs, MTB amplification
- PICC related paradoxical embolus
Timeline of Events

• **11/12/2013**: Phenotypic drug susceptibility testing (CDC and National Jewish) available
  – Indirect agar proportion method
  – Confirming resistance to INH, rifampin/rifabutin, PZA, ethambutol
  – Additional resistance detected to ethionamide
**Phenotypic DST – CDC & NJMC**

**NJMC** (7H11 Agar proportion method)

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>MIC ≤ 4.0 mcg/L</td>
<td>‘susceptible’</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>MIC ≤ 60</td>
<td>‘susceptible’</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>MIC ≤ 0.12 mcg/mL</td>
<td>‘susceptible’</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>MIC ≤ 4.0 mcg/mL</td>
<td>‘susceptible’</td>
</tr>
</tbody>
</table>

**CDC** (Indirect agar proportion, 7H10; MGIT 960)

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide</td>
<td>100 %</td>
<td>‘Resistant’</td>
</tr>
<tr>
<td>Isoniazid 0.2 ug/ml</td>
<td>100 %</td>
<td>‘Resistant’</td>
</tr>
<tr>
<td>Isoniazid 1.0 ug/ml</td>
<td>100 %</td>
<td>‘Resistant’</td>
</tr>
<tr>
<td>Isoniazid 5.0 ug/ml</td>
<td>100 %</td>
<td>‘Resistant’</td>
</tr>
<tr>
<td>Rifampin 1.0 ug/ml</td>
<td>100 %</td>
<td>‘Resistant’</td>
</tr>
<tr>
<td>Ethambutol 5.0 ug/ml</td>
<td>100 %</td>
<td>‘Resistant’</td>
</tr>
<tr>
<td>Streptomycin 2.0 ug/ml</td>
<td>0 %</td>
<td>‘Susceptible’</td>
</tr>
<tr>
<td>Streptomycin 10.0 ug/ml</td>
<td>0 %</td>
<td>‘Susceptible’</td>
</tr>
<tr>
<td>Rifabutin 2.0 ug/ml</td>
<td>3.33 %</td>
<td>‘Susceptible’</td>
</tr>
<tr>
<td>Cloprofloxacine 2.0 ug/ml</td>
<td>0 %</td>
<td>‘Susceptible’</td>
</tr>
<tr>
<td>Kanamycin 5.0 ug/ml</td>
<td>0 %</td>
<td>‘Susceptible’</td>
</tr>
<tr>
<td>Ethionamide 10.0 ug/ml</td>
<td>66.67%</td>
<td>‘Resistant’</td>
</tr>
<tr>
<td>Capreomycin 10.0 ug/ml</td>
<td>0 %</td>
<td>‘Susceptible’</td>
</tr>
<tr>
<td>PAS 2.0 ug/ml</td>
<td>0 %</td>
<td>‘Susceptible’</td>
</tr>
<tr>
<td>Ofloxacin 2.0 ug/ml</td>
<td>0 %</td>
<td>‘Susceptible’</td>
</tr>
<tr>
<td>Amikacin 4.0 ug/ml</td>
<td>0 %</td>
<td>‘Susceptible’</td>
</tr>
</tbody>
</table>

Susceptibility Testing Method: MGIT 960
Change in Abx therapy – November 2013

• Medical Therapy:
  – Dropped ethionamide
    • added linezolid 600 mg daily
  – Continued:
    • Cycloserine
    • Amikacin IV
    • Moxifloxacin
    • PZA
• Re-aspiration of left pleural space negative for AFB

• Repeat CT scan with decreased cavity size, less infiltrate, and healed bronchopleural fistula
  – (image)

• Infection prevention plan for operative plan developed

• Aggressive stroke rehabilitation program
Repeat CT 12/3/2013
2014 Hospital Course

• January 16, 2014: Successful repair of TOF
  – using Gore-Tex VSD patch
  – Right ventricular outflow tract resection
  – 24-mm pulmonary homograft
  – Suture closure of atrial septal defect

• AFB x 3 during intubation
  – 1 of 3 rare AFB, culture negative

• CT chest/CXR - images
Repeat CT 1/22/14
Chest XR Comparison

AUGUST 2013

MAY 2014
Summary Timeline

8/23/13 Admission Sputum smear & Cx (+)
8/24/13 Left pleural effusion and sputum smear and Cx (+)
8/30/13 Molecular resistance returned from CDC
9/26/13 Sputum smear & Cx (-)
12/11/14 Repeat thoracentesis, smear and Cx (-)
1/16/14 TOF repair
1/17/14 ET aspirate smear positive (1 of 3), Cx (-)
1/30/14 Sputum smear & Cx (-)
Hospital Discharge / Outpatient Plan

Discharged to host Ohio family on 3/20/14
Outside of Cleveland

• Medical Therapy:
  – Cycloserine 250mg po bid (adjusted to once daily via TDM)
  – Linezolid 600mg po daily (added 12/19/13)
  – Amikacin 900mg IV intermittent
  – Moxifloxacin 400mg po daily
  – PZA 1g po daily

• Monitoring of therapy by TDM (Univ. of Florida)
  – Cycloserine levels dosing adjustment
  – Amikacin via intermittent dosing
    • Renal function remained stable and serial audiograms revealed no hearing loss

• DOT via Huron County, Ohio Dept. Health
Question # 3

• Role of thoracic surgery for this MDR TB patient (with appropriate PFTS)?
  – Areas of concern include
    • Poor drug delivery to the hypoplastic left lung?
    • Sequestered area for evolution of XDR-TB?

1. Recommend resectional thoracic surgery (if PFTs ok) with decortication
2. Left pneumonectomy
3. Medical abx management alone
4. Pleural window creation for chronic drainage
5. Other?
Additional Points for Discussion

– CCF Surgeons felt surgical morbidity in the setting of negative cultures and resolution of the BPF to be high

– Postoperative access to thoracic surgery resources in Haiti is non-existent if there are complications that surgically need to be addressed.
Other pertinent issues

• Patient not able to remain in US
  – Host family not able to continuing hosting patient (no other families available to sponsor pt)
  – no funding

• Transition of care from US to Haiti – raising concerns for:
  – Patient wishes and autonomy
    • His desire to return to Haiti and be with family
    • Better access and follow up in US (best chance for success?)

  – Resource poor vs. resource rich environments
    • Transition of care to TB Centers (with MDR capacity) in Haiti - GHESKO or PIH
      – Linezolid, newer FQs, not available; very limited injectables
      – Thoracic surgery not available
      – Laboratory monitoring limited
      – Other logistics
        » Ensuring DOT
        » housing closer to TB center
        » center in home town of Hinche (via PIH)
Question # 4

- If patient returns to Haiti which approach seems most feasible for continuation of abx in Haiti (based on local drug availability) at GHESKO or PIH
  - linezolid, moxifloxacin, amikacin – not available
  - Continuation of cycloserine, PZA

1. Substitute with ciprofloxacin (or ofloxacin), PAS with continuation of cycloserine & PZA
2. Substitute with ciprofloxacin (or ofloxacin), streptomycin with continuation of cycloserine & PZA
3. Substitute with ciprofloxacin (or ofloxacin), PAS, clofazimine (unclear if available), streptomycin with continuation of cycloserine & PZA
4. Prohibit transfer back to Haiti until treatment for MDR TB has been completed (although funding remains a barrier)
5. Other options
Other points for discussion?