Multidrug-resistant Tuberculosis

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Clinical Intensive
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Objectives

• Describe the national and global epidemiology of MDR and XDR-TB
• Recognize who is at higher risk for MDR TB
• Discuss interpretation of molecular tests for drug resistance
• List the general principles of MDR/XDR-TB treatment
• Discuss the challenges in managing contacts of MDR/XDR-TB
• Identify resources for education, training, and expert consultation

Terminology

• Mono-resistant: resistant to only one drug
• Poly-resistant: resistant to more than one drug, but not the combination of INH and RIF
• Multidrug-resistant (MDR): resistant to at least INH and RIF
• Pre-extensively drug-resistant (Pre-XDR): MDR plus resistance to fluoroquinolone (FQ) or a second-line injectable (Amikacin, Kanamycin, or Capreomycin)
• Extensively drug-resistant (XDR): MDR-TB plus resistance to a FQ and at least one second line injectable
Global MDR Burden

- 2014 Estimate: 480,000 incident cases
  - Half from China, India and Russia
- Surveillance varies by country and region
  - Resistance surveys vs continuous surveillance
  - National vs subnational
  - 2015: Data from 79% of countries since 1994

Estimated Number of MDR-TB Cases Among Notified TB Patients, 2014

Percentage of New TB Cases with MDR TB, 2014

Overall: 3.3%
Percent of Previously treated cases with MDR-TB, 2014

Overall: 20%

In 2014, 12% of new and 58% of retreatment TB cases tested for MDR

XDR TB

- 9.7% of MDR TB cases
- 105 countries have reported at least 1 case
- “TDR” reports from Iran and India
Number of patients with XDR-TB started on treatment, 2014

Total = 4,044

Primary Anti-TB Drug Resistance
United States, 1993 – 2014*

<table>
<thead>
<tr>
<th>Year</th>
<th>Isoniazid</th>
<th>MDR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>1995</td>
<td>8</td>
<td>1.3</td>
</tr>
<tr>
<td>1997</td>
<td>4</td>
<td>0</td>
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<tr>
<td>1999</td>
<td>2</td>
<td>0</td>
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<tr>
<td>2001</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2003</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2005</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2007</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
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<td>0</td>
</tr>
<tr>
<td>2011</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Updated as of June 5, 2015.

Note: Based on initial isolates from persons with no prior history of TB. Multidrug-resistant (MDR) TB is defined as resistance to at least isoniazid and rifampin.

Primary Isoniazid Resistance in U.S.-born vs. Foreign-born Persons
United States, 1993 – 2014*

<table>
<thead>
<tr>
<th>Year</th>
<th>U.S.-born</th>
<th>Foreign-born</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>12</td>
<td>10.2</td>
</tr>
<tr>
<td>1995</td>
<td>8</td>
<td>7.5</td>
</tr>
<tr>
<td>1997</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>1999</td>
<td>2</td>
<td>0</td>
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<tr>
<td>2001</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2003</td>
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<td>0</td>
</tr>
<tr>
<td>2005</td>
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<td>0</td>
</tr>
<tr>
<td>2007</td>
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<td>2009</td>
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<td>0</td>
</tr>
<tr>
<td>2011</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Updated as of June 5, 2015.

Note: Based on initial isolates from persons with no prior history of TB.
Primary MDR TB in U.S.-born vs. Foreign-born Persons United States, 1993 – 2014*

% Resistant

>90% of MDR cases in foreign-born

XDR TB Case Count Defined on Initial DST* by Year, 1993 – 2014**

Case Count

Year of Diagnosis

Multidrug-resistant TB Cases California, 1995-2014

Number of MDR cases

Pct MDR cases

* Drug susceptibility test.
** Updated as of June 5, 2015.
Note: Multidrug-resistant TB (MDR TB) is defined as resistance to isoniazid and rifampin. Extensively drug-resistant TB (XDR TB) is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
Recognition: Who Is At Higher Risk of MDR-TB?

- History of previous TB treatment, particularly if recent
- Poor response to standard 4-drug treatment
  - Culture remains (+) after 2 months treatment
- Known exposure to MDR-TB case
- HIV (+)
  - Higher incidence of Rifampin mono resistance

Recognition: Who Is At Higher Risk of MDR-TB?

- Foreign born arrived in U.S. within last 2 years
- Immigration from or recent extended travel to country with > 2% MDR among cases from that country diagnosed in California/U.S.
- These countries* are:
  - India
  - Laos
  - Russia and other former Soviet states
  - Korea
  - Peru
  - Central America
  - Burma
  - Ecuador
  - Dominican Republic
- Other state or locally identified risk groups, including:
  - Hmong refugees
  - Persons of Tibetan origin

*California data from 2013-2015 and U.S. data from 2010-2013
†Current U.S. data are available from the CDC, Division of TB Elimination (DTBE) (www.cdc.gov/tb)

High-risk for MDR: Action Steps

- Obtain molecular test for drug resistance
  - Xpert MTB/RIF, (pyro)sequencing, Hain line-probe test, or other
- Consider initiation of expanded regimen (rare in era of molecular testing)
  - Contact of MDR-TB case with active TB
  - Immigrant with history of extensive treatment for TB in the past and again has active TB
  - Extended time to resistance information
Molecular Testing for Drug Resistance

### Molecular Testing: Drugs/Loci

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Gene/locus</th>
<th>Sensitivity (sequencing)</th>
<th>Specificity (sequencing)</th>
<th>Assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>katG</td>
<td>86.0</td>
<td>99.1</td>
<td>Hain, PSQ, MDDR</td>
</tr>
<tr>
<td>INH and Ethionamide</td>
<td>inhA promoter</td>
<td>4.5</td>
<td>100</td>
<td>PSQ</td>
</tr>
<tr>
<td>INH</td>
<td>fabG1</td>
<td>78.8</td>
<td>94.3</td>
<td>Hain, PSQ, MDDR</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>rpoB</td>
<td>97.1</td>
<td>97.4</td>
<td>Xpert, Hain, PSQ, MDDR</td>
</tr>
<tr>
<td>Ethambutol (EMB)</td>
<td>embB</td>
<td>79.0</td>
<td>99.6</td>
<td>Hain, PSQ, MDDR</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>pncA</td>
<td>90.9</td>
<td>98.4</td>
<td>Hain, PSQ, MDDR</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>gyrA</td>
<td>55.2</td>
<td>91.0</td>
<td>MDDR</td>
</tr>
<tr>
<td>Capreomycin (CAP)</td>
<td>rrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tlyA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Types of mutations

**Silent (synonymous)**
- Nucleic acid change
- No amino acid change
- Not associated with drug resistance generally
  - 514 [TTC \(\rightarrow\) TTT] mutation in rpoB is the most common silent mutation

**Missense (nonsynonymous)**
- Nucleic acid change
- Amino acid change
- Some are associated with resistance
**Molecular Testing for Rifampin (rpoB)**

- Rifampin cornerstone of TB treatment
  - Resistance requires a longer duration of therapy
  - Rif resistance without INH resistance rare
    Rif resistance = MDR

**Xpert Probes: Coverage of rpoB**

- Most common silent mutation (514 TTT)
- Most common resistance mutation (531 TTG)

<table>
<thead>
<tr>
<th>Probe Position</th>
<th>Coverage of rpoB</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probe B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probe C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probe D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probe E</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test Results**

- **Legend**
  - F: Probe F
  - C: Probe C
  - B: Probe B
  - A: Probe A
  - QC: QC

<table>
<thead>
<tr>
<th>Probe</th>
<th>Sample Size</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe F</td>
<td>POS</td>
<td>PASS</td>
</tr>
<tr>
<td>Probe C</td>
<td>30.6</td>
<td>POS</td>
</tr>
<tr>
<td>Probe B</td>
<td>35.5</td>
<td>POS</td>
</tr>
<tr>
<td>Probe A</td>
<td>0.0</td>
<td>NED</td>
</tr>
<tr>
<td>QC</td>
<td>0.0</td>
<td>NED</td>
</tr>
</tbody>
</table>
### Xpert Performance

**Rifampin Resistance**

- **Pooled median sensitivity:**
  - 95% (95% CrI: 90, 97)
- **Pooled median specificity:**
  - 98% (95% CrI: 97, 99)


### Number and Proportion MDR TB by Country/Region of Origin, CA 2011–2015

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>No.</th>
<th>%</th>
<th>PPV (99% spec)</th>
<th>PPV (98% spec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Former Soviet Republics</td>
<td>5</td>
<td>12.2</td>
<td>93%</td>
<td>87%</td>
</tr>
<tr>
<td>Laos</td>
<td>6</td>
<td>5.1</td>
<td>84%</td>
<td>72%</td>
</tr>
<tr>
<td>Burma</td>
<td>2</td>
<td>3.4</td>
<td>77%</td>
<td>63%</td>
</tr>
<tr>
<td>Japan</td>
<td>1</td>
<td>3.2</td>
<td>76%</td>
<td>61%</td>
</tr>
<tr>
<td>India</td>
<td>12</td>
<td>3.1</td>
<td>75%</td>
<td>60%</td>
</tr>
<tr>
<td>Guatemala</td>
<td>5</td>
<td>3.0</td>
<td>75%</td>
<td>60%</td>
</tr>
<tr>
<td>Korea (N&amp;S)</td>
<td>7</td>
<td>2.9</td>
<td>74%</td>
<td>59%</td>
</tr>
<tr>
<td>Peru</td>
<td>1</td>
<td>2.6</td>
<td>72%</td>
<td>56%</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>1</td>
<td>2.0</td>
<td>66%</td>
<td>50%</td>
</tr>
<tr>
<td>Philippines</td>
<td>27</td>
<td>1.7</td>
<td>54%</td>
<td>37%</td>
</tr>
<tr>
<td>Vietnam</td>
<td>15</td>
<td>1.4</td>
<td>57%</td>
<td>40%</td>
</tr>
<tr>
<td>China (incl Taiwan)</td>
<td>7</td>
<td>1.2</td>
<td>54%</td>
<td>37%</td>
</tr>
<tr>
<td>United States</td>
<td>13</td>
<td>0.8</td>
<td>44%</td>
<td>28%</td>
</tr>
<tr>
<td>Cambodia</td>
<td>1</td>
<td>0.7</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Mexico</td>
<td>11</td>
<td>0.6</td>
<td>36%</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Countries with >20 cases tested for MDR*
MDR TB Cases by Country/Region of Origin and Years in the US, CA 2011-2015

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Total MDR TB cases</th>
<th>≤ 2 years in US No. (%)</th>
<th>&gt;2 years in US No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Countries (excl US)*</td>
<td>103</td>
<td>30 (3.7)</td>
<td>71 (1.2)</td>
</tr>
<tr>
<td>Former Soviet Republics</td>
<td>5</td>
<td>2 (33.3)</td>
<td>3 (6.6)</td>
</tr>
<tr>
<td>Vietnam*</td>
<td>13</td>
<td>9 (7.5)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>China (incl Taiwan)*</td>
<td>7</td>
<td>5 (8.6)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Philippines*</td>
<td>27</td>
<td>8 (4.0)</td>
<td>19 (1.4)</td>
</tr>
<tr>
<td>Guatemala</td>
<td>5</td>
<td>1 (3.9)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>India</td>
<td>12</td>
<td>3 (3.3)</td>
<td>9 (8.2)</td>
</tr>
<tr>
<td>All Other Countries</td>
<td>10</td>
<td>2 (1.1)</td>
<td>8 (0.9)</td>
</tr>
<tr>
<td>Mexico</td>
<td>11</td>
<td>0 (0.0)</td>
<td>11 (0.7)</td>
</tr>
<tr>
<td>Korea, North and South</td>
<td>7</td>
<td>0 (0.0)</td>
<td>7 (1.2)</td>
</tr>
<tr>
<td>Laos</td>
<td>6</td>
<td>0 (0.0)</td>
<td>5 (4.6)</td>
</tr>
</tbody>
</table>

* Difference is statistically significant

Number and % MDR among foreign-born TB patients in the U.S., 2010–2013

<table>
<thead>
<tr>
<th>Country of origin</th>
<th>Total TB cases*</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ukraine</td>
<td>93</td>
<td>12</td>
<td>12.9</td>
</tr>
<tr>
<td>Laos</td>
<td>284</td>
<td>12</td>
<td>4.2</td>
</tr>
<tr>
<td>Peru</td>
<td>373</td>
<td>14</td>
<td>3.8</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>296</td>
<td>8</td>
<td>2.7</td>
</tr>
<tr>
<td>Ecuador</td>
<td>307</td>
<td>8</td>
<td>2.6</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>461</td>
<td>11</td>
<td>2.4</td>
</tr>
<tr>
<td>Burma / Myanmar</td>
<td>425</td>
<td>9</td>
<td>2.1</td>
</tr>
<tr>
<td>India</td>
<td>2,122</td>
<td>40</td>
<td>1.9</td>
</tr>
<tr>
<td>Vietnam</td>
<td>2,002</td>
<td>32</td>
<td>1.6</td>
</tr>
<tr>
<td>China</td>
<td>1,478</td>
<td>23</td>
<td>1.6</td>
</tr>
<tr>
<td>Haiti</td>
<td>755</td>
<td>11</td>
<td>1.5</td>
</tr>
<tr>
<td>Philippines</td>
<td>3,068</td>
<td>39</td>
<td>1.3</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>635</td>
<td>7</td>
<td>1.1</td>
</tr>
<tr>
<td>Guatemala</td>
<td>777</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Mexico</td>
<td>5,542</td>
<td>37</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention, Division of Tuberculosis Elimination, National Tuberculosis Surveillance System, Bob Pratt

How to interpret results of molecular tests for resistance
Case 1

- 70 yo asymptomatic man from India with abnormal preimmigration CXR, no TB history
- Domestic CXR with multifocal infiltrates
- Sputum smear positive x 3
- Xpert positive: rifampin resistant

**What do you do next?**
- Start MDR treatment
- Order pyrosequencing or MDDR
- Start RIPE
- Repeat Xpert on another specimen
- Start treatment for monoRif resistance

---

Case 1

- Treatment held; PSQ available within 2 days and clinically stable
- Pyrosequencing:
  - katG mutation: INH R
  - rpoB 531TTG mutation: RIF R
  - gyrA (FQ): no mutations
  - rrs (amikacin): no mutations

**What do you do next?**
- Start MDR treatment
- Order MDDR
- Start RIPE
- Repeat Xpert on another specimen
- Order second line DSTs
- Cancel DSTs (already have molecular results)

---

Case 2

- 70 yo man from Mexico in US x 25 years with 4 weeks of cough, no TB history
- CXR with multifocal infiltrates
- Sputum smear positive x 3
- Xpert positive, rifampin resistant

**What do you do next?**
- Start MDR treatment
- Order pyrosequencing or MDDR
- Start RIPE
- Repeat Xpert on another specimen
- Start treatment for monoRif resistance
Case 2

- RIPE started
- PSQ:
  - \textit{katG/inhA}: no mutation
    - INH Sens
  - \textit{rpoB}: 514TTT silent mutation: RIF Sens

How to interpret molecular test for resistance

- Put into clinical and epidemiologic context!
- Confirm non-sequencing tests (e.g., Xpert) with sequencing test
- Consider Rif resistance on Xpert to be MDR (not just rifampin monoresistant)
- Can usually treat based on sequencing test results; follow the growth based DST results

Limitations / Areas for Caution

- Molecular tests vs. DST discordance
  - “Disputed” mutations
  - Undescribed mutations outside of loci in current molecular tests \(\rightarrow\) resistance
  - Emerging resistance in mixed populations may not be detected
Case 3

- 23 year old male from Mexico diagnosed with smear-positive, pulmonary TB
- PSQ results
  - katG mutation: “Associated with INH resistance”
  - rpoB mutation 526AAC: “Not associated with RIF or RFB resistance”
- Growth-based DST results: INH resistance only
- Treated with RIF, EMB, PZA for 9 months
- End of treatment sputum: smear and culture-positive

Commercial Line Probe Assays

- For detection of M. tuberculosis complex and mutations associated with drug resistance
- Genotype MTBDRplus 2.0 from Hain Lifescience
  - Rifampin and INH resistance
- Genotype MTBDRsl 1.0 and 2.0
  - FQ (gyrA gyrB); EMB (embB); amikacin (rrs); kanamycin (eis)
- Not FDA approved

Basic steps: Choosing a regimen

- Decision: Begin empiric MDR regimen
- Ask for help: Expert consultation
- Empiric (expanded) regimen for MDR:
  - 4 first-line + FQ + injectable
  (+ consider additional second-line drug)
How many drugs for MDR?

Goal: 4-6 likely effective drugs
 optimally at least 5

- Recent studies suggest better outcomes with at least 5 drugs
- Expert input:
  - Consider more if extensive disease and/or resistance
  - Four may be sufficient with limited disease and/or limited resistance
- [WHO 2011 – “at least 4 likely effective drugs”]

Building an Individualized Regimen for MDR-TB

STEP 1
Use any available

<table>
<thead>
<tr>
<th>First-line drugs</th>
<th>Fluoroquinolones</th>
<th>Injectable agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide</td>
<td>Levofloxacin</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Moxifloxacin</td>
<td>Capreomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kanamycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptomycin</td>
</tr>
</tbody>
</table>

+ OR

1. Not available in U.S.
2. SM: use only if not previously used and if documented susceptibility

Building a Regimen for MDR-TB (2)

STEP 2
Pick one or more of these

<table>
<thead>
<tr>
<th>Oral second-line drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycloserine</td>
</tr>
<tr>
<td>Ethionamide</td>
</tr>
<tr>
<td>PAS</td>
</tr>
<tr>
<td>Linezolid3</td>
</tr>
</tbody>
</table>

+ OR

3. Although considered a third-line drug, many experts now use LZD as a second-line drug option
Consider use of these third-line drugs:
- Bedaquiline
- Delamanid
- Clofazimine
- Imipenem
- Meropenem/Clavulanate
- Amoxicillin/Clavulanate
- Clarithromycin
- High-dose INH

If there are not 4-6 drugs available in the above categories, consider third-line drugs in consultation with an MDR-TB expert.

**Classification: U.S. vs. WHO**

**New WHO Guidelines 2016**

- Conventional MDR treatment:
  - 5 drugs, including PZA
- Demoted:
  - PAS and EMB
- Promoted:
  - Clofazimine, linezolid, INH high-dose
- Short Course

http://www.who.int/entity/tb/areas-of-work/drug-resistant-tb/MDRTBguidelines2016.pdf?ua=1
“Bangladesh Regimen”
Short course treatment for MDR

• 4-6 m: AK – MFX – ETA – CFZ – PZA – INH_{Hi-dose} – EMB
• 5 m: MFX – CFZ – PZA – EMB
• Observational data impressive (85-90% cure)
• RCTs ongoing
• Contraindications: resistance to any drug in regimen, extrapulmonary disease, pregnancy
• Should this be used in the U.S.?


Other considerations when choosing drugs
Beyond susceptibility results, consider:
• Cross-resistance (table page 76)
• Avoid drugs used previously
• Side effect profile

Treatment Duration

• Survival Guide – Expert consensus for U.S. Setting:
  – Use culture conversion to guide minimum duration
  – Intensive phase: at least 6 mo beyond culture conversion for use of injectable agent
  – Total duration: at least 18 months beyond culture conversion

• WHO 2011 and 2016 Guideline:
  – Intensive phase at least 8 months
  – Total duration at least 20 months
  (if no prior rx for MDR; if prior MDR rx at least 24 months)
• 2003 ATS/CDC/IDSA guidelines: 18-24 mo
Treatment regimens

- Suggestions based on pattern of drug resistance
- Pre-XDR and XDR recommend longer duration (at least 24 mo. post culture conversion)

Medication Fact Sheets

- Drug class/trade name
- Activity against TB
- Cross-resistance
- Dose (adult, peds, renal)
- Route of administration
- Preparation/storage
- Pharmacokinetics
- Oral absorption/metabolism
- CSF penetration
- Special circumstances
- Adverse reactions/contraindications
- Monitoring
- Costs/patient education

Bedaquiline

- First new class of TB medication approved in 40 years
- Selective mycobacterial ATP synthase inhibitor
- RCTs showed significantly more patients culture converted at 2 months, BUT also showed significantly more deaths in bedaquiline arm
  - BDQ: 9 of 79 (11.4%) versus Placebo: 2 of 81 (2.5%)
  - Deaths seemed unrelated to bedaquiline
- Approved for pulmonary MDR TB in adults when an “effective regimen cannot otherwise be provided”
**Bedaquiline Challenges**

- Cost: $30,000 (or $23,000 for public health depts in outpatient setting only) for 24 weeks
- Prolongs QTc
  - Additive with MFX, clofazimine
  - Weekly EKG recommended
- Extremely long terminal elimination half-life
  - 4-5 months

**Regimens for XDR-TB**

- Treatment choices are limited
- Bedaquiline, Linezolid and any remaining injectable become the mainstay of treatment
- Add whatever oral medications are left to which there is *in vitro* susceptibility
- Surgery if disease is localized
- Nearly all patients are treatable and curable

**Surgery?**

- No hard and fast rules; WHO: Surgery “may be used”
- Metaanalysis suggests success
- Consider if:
  - Very extensive resistance
  - Residual large cavity
  - Predominantly one-sided disease
  - Previous MDR treatment failure

**MDR-TB Clinical Case Management**

- Seek consultation with MDR-TB expert as soon as multidrug resistance known
- Use daily DOT throughout entire treatment course
  - No intermittent therapy for drug resistance!!
- Use case management tools (drug-o-gram) to follow serial changes in drugs, bacteriology, CXR, toxicities
- Optimize management of underlying medical conditions and nutritional status (i.e. diabetes)

**MDR-TB Clinical Case Management (2)**

- Isolate until 3 consecutive sputa AFB smears are negative and there has been a good response to treatment
- Consider isolation until culture negative in certain situations
- Usually outpatient care; hospitalization can be helpful
- Tailor toxicity monitoring to specific drugs employed
Therapeutic Drug Monitoring

- Cycloserine:
  - absorption highly variable
  - therapeutic and toxic levels are very close
  - drug levels are highly recommended
  - Draw 2 hours after dose

- Injectable:
  - if renal compromise, significantly over or under weight, or elderly
  - Some experts recommend obtaining levels routinely
  - peak and/or trough levels

Recommended MDR-TB Monitoring for Efficacy

- Collect sputum periodically (e.g., monthly) during treatment once culture negative
- Obtain end-of-treatment sputum for smear and culture
- Perform CXR periodically during treatment (e.g., quarterly) and at end of treatment
- Monitor minimum of 2 years following treatment (quarterly during first year, every 6 months during second year)
MDR-TB Laboratory Monitoring

- As soon as isolate is known resistant to INH and RIF, order second-line drug susceptibilities
- Repeat susceptibilities on cultures that remain positive after 2-3 months
- Repeat susceptibility for EMB/PZA if susceptible at baseline and patient received ≥4 weeks of first-line treatment on positive cultures obtained near start of MDR treatment
Directly Observed Therapy (DOT) for MDR-TB

- Essential
- Improved overall cure rates, including MDR cases
- Reduction in community prevalence of MDR

Orenstein et al Lancet Inf Dis 2009; Weis et al NWM 1994; 330, 1179

Common Side Effects

<table>
<thead>
<tr>
<th>G.I. complaints</th>
<th>Ethionamide, PAS, Quinolones, Clofazimine, Rifabutin, Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss, vestibular toxicity</td>
<td>Injectables</td>
</tr>
<tr>
<td>Renal insufficiency/Electrolyte Abn</td>
<td>Injectables</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>PZA, PAS, Rifabutin, Ethionamide, Quinolones</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Linezolid, INH, Quinolones, Ethionamide, Cycloserine</td>
</tr>
<tr>
<td>Neuropsychiatric: depression, agitation, psychosis, difficulty concentrating, insomnia</td>
<td>Cycloserine, Quinolones, Ethionamide</td>
</tr>
<tr>
<td>Rash</td>
<td>All</td>
</tr>
<tr>
<td>Visual changes</td>
<td>EMB, Rifabutin, Linezolid</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Ethionamide, PAS</td>
</tr>
<tr>
<td>Headache</td>
<td>Quinolones, Cycloserine, Ethionamide, EMB</td>
</tr>
</tbody>
</table>

Prevention

- Preventing acquired drug resistance
  - DOT and daily therapy as appropriate
- Preventing transmission of MDR-TB to contacts
  - Effective treatment, isolation until noninfectious
- Preventing progression to active disease in infected MDR-TB contacts
  - MDR LTBI treatment and monitoring
Isolation (CDPH/CTCA Guidelines)

• Patients with pulmonary MDR-TB should be considered infectious until:
  ▪ An appropriate MDR regimen has been initiated and tolerated for 2 weeks AND
  ▪ A favorable clinical response has occurred AND
  ▪ 3 consecutive sputum smears are documented AFB negative

Preventing Progression to Active TB

• Little published data on LTBI treatment for MDR-TB contacts; No randomized trials
• CDC guidance last in 1992
• Contact investigation and management principles same as drug susceptible:
  – Drug resistant TB is not more infectious, but duration can be longer and consequences are greater
  – Consider infectiousness of index case, duration/intensity of contact, immune status of contact, LTBI test results
  – Rule out active disease prior to starting LTBI treatment

Treatment Regimens for MDR-TB Contacts

• FQ monotherapy
• FQ + EMB
• Monitor for 2 years only – acceptable
• FQ + PZA – very poorly tolerated
• PZA + EMB
• Other combinations? Duration?
Fluoroquinolones for MDR Contacts

- Published data from 2 MDR outbreaks in Chuuk:
  - 104 of 119 received LTBI treatment x 12 months
    - Adults: MFX + EMB (n=24) or MFX/LFX alone (n=51)
    - Children: LFX + EMB (N=17) or LFX + Ethionamide (n=12)
  - 11 stopped early; 6 received >6 mos
  - 0 cases in treated vs 3 among 15 refused (36 mo f/u)

Resources

Resources: RTMCCs

- Francis J. Curry International Tuberculosis Center
  1-877-590-NOTB or 1-877-590-9582
  www.currytbcenter.ucsf.edu

- Heartland National Tuberculosis Center
  1-800-TEX-LUNG or 1-800-839-5864
  www.heartlandntbc.org

- New Jersey Medical School Global Tuberculosis Institute
  1-800-4TB-DOCS or 1-800-482-3627
  www umdnj.edu/globaltb

- Southeastern National Tuberculosis Center
  1-800-4TB-INFO or 1-800-482-4636
  http://sntc.medicine.ufl.edu

- Mayo Clinic Center for Tuberculosis
  855-360-1468
  http://centerfortuberculosis.mayo.edu/
(Mostly) International MDR Resources

- Partners in Health Guide (2013):
- WHO MDR Guides:
    http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf
  - Guideline (2016):
- CDC Bedaquiline Guideline (2013):

California Resources

- MDR-TB Service
  - Provides clinical consultation, case management, CI assistance – 510-620-3000
- CA Microbial Diseases Lab
  - pyrosequencing for drug resistance
  - phenotypic DST for first-line drugs and amikacin, moxifloxacin, capreomycin, and ethionamide

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Origin of Drug Resistance

Random Naturally Occurring Resistance in Bacterial Population

- INH = 1 in $10^6$
- RMP = 1 in $10^8$
- EMB = 1 in $10^6$
- Strep = 1 in $10^6$

\[ \text{INH and RIF} = 10^6 \times 10^8 = 1 \text{ in } 10^{14} \]

Random drug-resistant mutants in large (> $10^6$) bacterial population

Multidrug therapy works: No bacteria resistant to all 3 drugs

Monotherapy: INH-resistant bacteria grow

INH

RIF

PZA

INH

INH resistant organism

RIF resistant organism

PZA resistant organism
When treated with just one drug, resistant bacteria begin to grow.

Spontaneous mutations to other drugs (RIF) develop as bacilli grow to >10^8 organisms.

INH mono-resist mutants killed by adding RIF, but RIF-resist mutants proliferate → MDR TB

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**Spread of MDR TB**

- “Biological Fitness” of the M. tb organism is not generally worsened by resistance
  - Studies have shown robust growth among RIF resistant and MDR strains
- Once created, drug resistant TB can spread to other people
  - The majority of global MDR TB (>70%) is among new patients (i.e., was transmitted and not acquired)

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**Criteria for Release from Isolation to High and Lower Risk Settings**

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Setting</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB case</strong></td>
<td>High risk</td>
<td>Three consecutive respiratory specimens collected on separate days, including at least one sputum or induced sputum, or both, are AFB smear negative, and no subsequent sputum specimen is AFB smear positive.</td>
</tr>
<tr>
<td><strong>New, MDR-TB case</strong></td>
<td>High risk</td>
<td>Three consecutive respiratory specimens collected on separate days, including at least one sputum or induced sputum, or both, are AFB smear negative, and no subsequent sputum specimen is AFB smear positive.</td>
</tr>
<tr>
<td><strong>Lower risk</strong></td>
<td>Lower risk</td>
<td>Three consecutive sputum specimens collected on separate days are AFB smear negative.</td>
</tr>
</tbody>
</table>

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**Notes:**

- *A patient may be considered for placement in a lower risk setting without meeting these criteria if no previously unexposed persons will be present (see section: Home isolation)*