Drug Resistant Tuberculosis: Pearls and other Considerations

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Objectives

• Review the current guidelines for the treatment of MDR TB disease
TB Therapy Drug Resistance Definitions

• **Poly-resistant TB**
  - Resistance to >1 drug
    - but not isoniazid and rifampin

• **Multi-Drug Resistant (MDR) TB**
  - Resistance to at least isoniazid and rifampin

• **Extensively Drug Resistant (XDR) TB**
  - MDR (INH & rifampin) + plus:
    - Resistance to a fluoroquinolone + plus:
    - Resistant to an injectable (kanamycin, streptomycin, amikacin)
Risk Factors for Drug-resistant TB

1. Previous TB therapy – especially with
   • Prior non-DOT based therapy
   • Patient non-compliance
   • Incomplete treatment, lack of documentation
   • Non-CDC, non-WHO endorsed standard regimens
   • Acknowledging for a patient – *TB therapy is difficult*
     • Prolonged treatment program
     • Many pills
     • Common drug intolerances

2. Contact with a patient with drug-resistant TB

Seaworth B. IDCNA Vol 16, No. 1, 73-105. March 2002
3. Persons from countries with higher rates of drug-resistant/MDR TB cases

More than 6% of new TB cases are MDR-TB in these locations:
- Azerbaijan, Baku City (22.3%)
- Kazakhstan (20%)
- Republic of Moldova (19.4%)
- Ukraine, Donetsk (16%)
- Russian Federation, Tomsk (15%)
- Uzbekistan, Tashkent (14.8%)
- Estonia (13.3%)
- Russian Federation, Mary El (12.5%)
- Latvia (10.8%)
- Lithuania (9.8%)
- Armenia (9.4%)
- Russian Federation, Orel (8.8%)
- China, Inner Mongolia (7.3%)
- China, Heilongjiang (7.2%)
- Georgia (6.8%)

Risk Factors for Drug-resistant TB - cont’d

4. Lack of response while on therapy:
   a. Clinical or radiologic progression
   b. MTB cultures remain (+) after 3 mo.

5. International TB endemic regions:
   a. Prolonged hospitalization (TB endemic regions / international)
   b. HIV co-infection (TB endemic regions / international)
   c. Lack of sustainable drug availability to patients through inadequate pharmaceutical supply chain and/or failure to provide free treatment

6. Overuse of fluoroquinolones in other infection syndromes that propagates fluoroquinolone-resistant TB (Respir inf., UTI)

7. Delays in diagnosing TB (inappropriate abx exposure)
M. tuberculosis complex resistant isolates

• If the isolate is resistant to any agent – Consider:
  • Confirming resistance by 2nd method or 2nd lab
  • Initiating testing of secondary agents to avoid delays

• If the isolate is resistant to only PZA consider:
  • Mycobacterium speciation
    • M. bovis is mono-PZA-resistant
      (most isolates of M. tuberculosis are PZA-susceptible)
  • Sequencing for pncA gene mutation
Pyrazinamide resistance – Sequencing of *pncA*

- Broth DST of PZA can overcall resistance
  - MGIT (up to 68% false resistance)
    - Piersimoni C et al., 2013, J Clin Microbiol. 51:291-4
    - Simons SO et al., 2012, J Clin Microbiol. 50: 428-34
  - VersaTREK (~70% false resistance)
    - Simner PS et al., manuscript in preparation

- Sequencing of the *pncA* gene from culture isolates can help
  - Mutations associated with resistance occur throughout this 558bp gene so sequence entire gene and promoter region
  - Performed by CDC, Mayo or the NYS DOH Wadsworth Center
Xpert MTB/RIF and Rifampin resistance

- Target is \textit{rpoB}: gene encoding beta subunit of bacterial RNA polymerase
- Mutations in an 81bp region of the \textit{rpoB} gene are responsible for \textasciitilde96\% of RIF resistance in \textit{Mtb};
- also predicts MDR TB since the majority of RIF-resistant isolates will also be INH-resistant
- Some false positive RIF resistance with Xpert
  - PPV is lower in low prevalence settings
  - CDC recommends reporting Xpert RIF-R as a preliminary result pending confirmation with sequencing; growth-based DST is still required
Molecular resistance testing for MTB at the CDC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Locus/Loci examined</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>rifampin</td>
<td>rpoB</td>
<td>97.1</td>
<td>97.4</td>
</tr>
<tr>
<td>isoniazid</td>
<td>inhA &amp; katG</td>
<td>86.0</td>
<td>99.1</td>
</tr>
<tr>
<td>fluoroquinolones</td>
<td>gyrA</td>
<td>79.0</td>
<td>99.6</td>
</tr>
<tr>
<td>kanamycin</td>
<td>rrs &amp; eis</td>
<td>86.7</td>
<td>99.6</td>
</tr>
<tr>
<td>amikacin</td>
<td>rrs</td>
<td>90.0</td>
<td>98.4</td>
</tr>
<tr>
<td>capreomycin</td>
<td>rrs &amp; tlyA</td>
<td>55.2</td>
<td>91.0</td>
</tr>
<tr>
<td>ethambutol</td>
<td>embB</td>
<td>78.8</td>
<td>94.3</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>pncA</td>
<td>86.0</td>
<td>95.9</td>
</tr>
</tbody>
</table>

Second Line TB Medications

• Less effective

• More expensive

• More toxic
Second Line TB Medications

- Fluoroquinolones
  - Moxifloxacin, Levofloxacin
- Aminoglycosides
  - Streptomycin, Amikacin & Kanamycin
- Capreomycin
- Linezolid
- Ethionamide
- Cycloserine
- Para-Aminosalicylic Acid (PAS)
New and other novel drugs for use (MDR- & XDR-TB) → a few other “arrows in the quiver”

New drugs

• Bedaquiline
• Delamanid

Older / less active

• Clofazimine
• Carbapenem/clavulanate
Principles of Drug-Resistant TB Management

- A single new drug should never be added to a failing regimen
- MDR/XDR treatment regimens are based on expert opinion, not clinical trials
- Several regimens exist based on different sites/guidelines
  - Drug Resistant TB, Survival Guide; Francis Curry TB Center / UCSF
  - New York City Dept. of Health, Clinical policies and protocols. *Bureau of Tuberculosis Control*, 2008
  - WHO Guidelines for the programmatic management of drug-resistant tuberculosis.
Treatment options, regimens and basic approaches for drug-resistant TB
Monoresistance – Isoniazid

- Rifampin, PZA, Ethambutol x 6-9 months

- Considerations for more extensive disease:
  - Treat 9 months
  - Add fluoroquinolone (moxifloxacin, levofloxacin) or injectable (e.g. amikacin)

- Examples: ND, Wisc. TB outbreaks
Mono-resistance - Rifampin

NYCHD

• Option 1: Induction - INH/PZA/EMB/inj/FQ x 2-3 mo. after culture conversion
  Continuation: INH/PZA/EMB+-/FQ x 12-14 mo. (18 total mo. preferred)

• Option 2: Induction - INH/PZA/SM+-/-EMB 2-3 mo. after culture conversion
  Continuation - INH/PZA/SM+-/-EMB x 3-5 mo. (9 mo. total)

Curry/UCSF

• Option 1: INH/EMB/PZA/FQ x 2 mo. then INH/EMB/FQ to complete 12-18 mo.

• Option 2: Option 1 +injectable for first 2 mo.

• Option 3: INH/PZA/SM( or other inj) x 9 mo.

WHO

• Treat as MDR TB
Mono-resistance to EMB, PZA, or SM

• Little impact on treatment efficacy
• Loss of EMB/SM does not change efficacy or treatment duration
• Loss of PZA: extend duration with INH/RIF by 3 mo. (9 mo. total)
Poly-resistant TB

- Resistance to >1 TB drug, but not INH & RIF
- Treatment should include as many 1st line drugs as possible + FQ and in some cases injectable
  - Composition and duration of therapy depended upon specific drug resistance profile
Approach to MDR-TB Management

• Include any active 1\textsuperscript{st} line drug, then add FQ and injectable (amikacin/kanamycin/SM/capreomycin)

• Add oral 2\textsuperscript{nd} line drugs to compose 4-6 drug regimen
  • Note: When restarting or revising therapy, always try to use at least 3 previously unused drugs to which there is demonstrated in vitro susceptibility (1 should be injectable)

• If there are not 4-6 active drugs available, then consider 3\textsuperscript{rd} line drugs (BDQ, clofazimine, carbapenem/clavulanate, high dose-INH)

• Surgery can be considered with complex cavitary disease or slow clinical response
Additional considerations

• “Low level” INH resistance
  • INH resistance at MIC 0.2 mg/L, but active at MIC 1.0mg/L
  • Consideration for 900 mg INH BIW/TIW weekly
  • Would not count INH as an “active” drug in regimen

• ~10-15 % rifampin resistant MTB may be susceptible to rifabutin (in vitro)
  • Rifabutin can be considered, but would not count as active drug
Composing an Effective Drug Treatment Program for MDR-TB

**STEP 1**

Begin with any first-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

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**Use any available**

**First-line drugs**
- Pyrazinamide
- Ethambutol

**One of these**

**Fluoroquinolones**
- Levofloxacin
- Moxifloxacin

**One of these**

**Injectable agents**
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

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Challenging
Composing an Effective Drug Treatment Program for MDR-TB

**STEP 2**

Add second-line drugs until you have 4–6 drugs (optimally at least 5) to which the isolate is susceptible (and preferably which have not been used to treat the patient previously)

Pick one or more of these

**Oral second-line drugs**

- Cycloserine
- Ethionamide
- PAS
- Linezolid

More challenging
Composing an Effective Drug Treatment Program for MDR-TB

**Step 3**

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

<table>
<thead>
<tr>
<th>Third-line drugs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline</td>
<td>Meropenem/Clavulanate</td>
</tr>
<tr>
<td>Delamanid⁴</td>
<td>Amoxicillin/Clavulanate</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Imipenem</td>
<td>High-dose INH</td>
</tr>
</tbody>
</table>

Most challenging
Extremely Drug resistant TB (XDR-TB)

• Resistance profile:
  • INH & rifampin = MDR strain, and:
  • A fluoroquinolone, and:
  • One of injectables (kanamycin, streptomycin, amikacin)

• Similar approach to MDR TB but may need to use 3rd line drugs

• Surgery should strongly be considered

Other consideration:

• Delays in starting expanded therapy until DST available is occasionally considered:
  
  • *A Judgement call* – *based on*:
    
    • *Stable disease* in immunocompetent host
    • No vulnerable contacts at home
    • MDR or XDR-TB case when DST pending and construction of active regimen is in doubt
    • Patient is NOT a flight risk
WHO MDR-TB treatment approaches – 2016: New and Old “pearls”

• **Regrouping** of 2nd & 3rd line TB drugs

• Rifampin-resistant TB treated as MDR-TB
  • Regardless if INH resistance confirmed or not

• Durations of therapy
  • **Intensive phase** of therapy: 8 months
  • **Total duration** of therapy: generally 20 months

• HIV Co-infected pts:
  • Start ART within 8 weeks of starting expanded TB therapy

• New options for **short course** (9-12 mo) therapy
<table>
<thead>
<tr>
<th>GROUP</th>
<th>DESCRIPTION</th>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>First-line oral anti-TB drugs</td>
<td>Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Rifabutin, Rifapentine</td>
</tr>
<tr>
<td>2</td>
<td>Injectable anti-TB drugs (injectable agents or parenteral agents)</td>
<td>Streptomycin, Kanamycin, Amikacin, Capreomycin</td>
</tr>
<tr>
<td>3</td>
<td>Fluoroquinolones (FQs)</td>
<td>Levofoxacin, Moxifloxacin, Gatifloxacin, Ofloxacin</td>
</tr>
<tr>
<td>4</td>
<td>Oral bacteriostatic second-line anti-TB drugs</td>
<td>Ethionamide, Prothionamide, Cycloserine, Terizidone, p-aminosalicylic acid, p-aminosalicylate sodium</td>
</tr>
<tr>
<td>5</td>
<td>Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents)</td>
<td>Bedaquiline, Delamanid, Linezolid, Clofazimine, Amoxicillin/Clavulanate, Imipenem/Cilastatin, Meropenem, High-dose isoniazid, Thioacetzone, Clarithromycin</td>
</tr>
</tbody>
</table>
Updated - WHO Classification of 2\textsuperscript{nd} and 3\textsuperscript{rd} line TB medications (use in RR-TB and MDR-TB)

| A. Fluoroquinolones\textsuperscript{2} | Levofloxacin | Moxifloxacin | Gatifloxacin | Lfx | Mfx | Gfx |
| B. Second-line injectable agents | Amikacin | Capreomycin | Kanamycin (Streptomycin)\textsuperscript{3} | Am | Cm | Km | (S) |
| C. Other core second-line agents\textsuperscript{2} | Ethionamide / Prothionamide | Cycloserine / Terizidone | Linezolid | Clofazimine | Eto / Pto | Cs / Trd | Lzd | Ctz |
| D. Add-on agents (not part of the core MDR-TB regimen) | Pyrazinamide | Ethambutol | High-dose isoniazid | Z | E | H\textsuperscript{h} |
| | Bedaquiline | Delamanid | Bdq | Dlm |
| D1 | \(p\)-aminosalicylic acid | Imipenem-cilastatin\textsuperscript{4} | Meropenem\textsuperscript{4} | Amoxicillin-clavulanate\textsuperscript{4} (Thioacetazone)\textsuperscript{5} | PAS | Ipm | Mpm | Amx-Clv (T) |

1. This regrouping is intended to guide the design of conventional regimens; for shorter regimens lasting 9-12 months the composition is usually standardized (See Section A).
2. Medicines in Groups A and C are shown by decreasing order of usual preference for use (subject to other considerations; see text).
3. Refer to the text for the conditions under which streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of extensively drug-resistant TB (XDR-TB)\textsuperscript{26}.
4. Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin.
5. HIV-status must be tested and confirmed to be negative before thioacetazone is started.
WHO Mgmt. approach to RR- and MDR-TB
- Conventional regimens

- Use at least 5 effective drugs during intensive phase
  - Include PZA and 4 core 2\textsuperscript{nd} line meds:
    - 1 - from \textbf{Group A} (fluoroquinolones)
    - 1 - from \textbf{Group B} (injectables)
    - At least 2 from \textbf{Group C}:
      - Ethionamide
      - Linezolid
      - Cycloserine
      - Clofazimine
WHO Mgmt. approach to RR- and MDR-TB
- Conventional regimens

• If not able to compose a regimen of 5 effective drugs from Groups A-C, then:
  • Select **D2 Drug**: Bedaquiline, Delamanid
  • Select **D3 Drugs** as needed: PAS, carbapenem-clavulanate, THA

• Notes:
  • Clarithromycin and other macrolides *no longer* recommended for TB therapy
  • Linezolid “promoted” / added to 2\textsuperscript{nd} line drugs
  • PAS “demoted” / removed (moved into D3)
Emergence of “Short Course” MDR TB Treatment options (9-12 months)

- is this ready for “Prime Time”??
Bangladesh short course trials

• Observational study
  • Used later generation quinolones (and in higher doses – gatifloxacin)
  • Combined (extensive) with other 2\textsuperscript{nd} line drugs (7 drugs early on)
  • Still included 1\textsuperscript{st} line drugs (EMB, PZA, INH; except RIF)
  • Pt population largely HIV neg.
Bangladesh Short Course MDR TB Regimen (observational study)

• 427 MDR TB patients enrolled

• Excluded patients previously treated with second-line TB drugs (> 1 mo)

• The most effective treatment regimen required a minimum of 9 months combination tx:
  • Gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout the 9 mo treatment period
  • Initial addition of prothionamide, kanamycin, and high-dose isoniazid for a min. of 4 mo intensive phase
  • Relapse-free cure of 87.9% (95% confidence interval, 82.7–91.6) among 206 patients

### TABLE 1. REGIMENS SEQUENTIALLY USED IN THE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS, BANGLADESH DAMIEN FOUNDATION PROJECTS

<table>
<thead>
<tr>
<th>Regimen (sequence)</th>
<th>Intensive Phase</th>
<th>Continuation Phase 1</th>
<th>Continuation Phase 2</th>
<th>Patients Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3* KCOEHZP</td>
<td>12 OEHZP</td>
<td>6 EP</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>3(+) KCOEHZP</td>
<td>12 OHEZP</td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>3(4) KCOEZP</td>
<td>12 OEZP</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>3(+) KCOEHZP</td>
<td>12 OHEZ</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>3(+) KCOEHZP</td>
<td>12 OHEZC</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>4(+) KCGEHZP</td>
<td>5 GEZC</td>
<td></td>
<td>206</td>
</tr>
<tr>
<td>Total number of patients enrolled</td>
<td></td>
<td></td>
<td></td>
<td>427</td>
</tr>
</tbody>
</table>

Definition of abbreviations: C = clofazimine; Col % = column percent; E = ethambutol; G = gatifloxacin; H = isoniazid; K = kanamycin; O = ofloxacin; P = prothionamide; Z = pyrazinamide.

* Numbers in front of phase indicate months. 3(4) indicates minimum of 3 mo, prolonged to 4 mo if no conversion by end of 3 mo. 3(+) indicates minimum of 3 mo, prolonged until conversion is achieved, if no conversion by the end of 3 mo. 4(+) indicates minimum of 4 mo, prolonged until conversion is achieved, if no conversion by the end of 4 mo. All drugs were given daily throughout under direct observation.
### Table 2. Daily Drug Dosages Used for Standardized Multidrug-Resistant Antituberculosis...  

<table>
<thead>
<tr>
<th>Drug</th>
<th>&lt;33 kg</th>
<th>33-50 kg</th>
<th>&gt;50 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanamycin*</td>
<td>500 mg</td>
<td>750 mg</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>600 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>Gatifloxacin†</td>
<td>400 mg</td>
<td>600 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>Prothionamide‡</td>
<td>250 mg</td>
<td>500 mg</td>
<td>750 mg</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>50 mg</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>200 mg</td>
<td>300 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Isoniazid high dose‡</td>
<td>300 mg</td>
<td>400 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>800 mg</td>
<td>800 mg</td>
<td>1,200 mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1,000 mg</td>
<td>1,500 mg</td>
<td>2,000 mg</td>
</tr>
</tbody>
</table>

*The kanamycin dosage was reduced by 25% for patients over 45 yr of age. Later, the dosage was given more precisely as 15 mg/kg body weight and was given only three times weekly rather than daily from the fourth month onward.

†Gatifloxacin was used at a lower dosage for the first 50 patients enrolled (200 mg up to 33 kg or 400 mg if over 33 kg)

‡For prothionamide and high-dose isoniazid, the highest dosing was given only to patients weighing over 55 kg (not 50 kg). The high dose of isoniazid was used with the gatifloxacin-based regimen, whereas the normal dose was given in all ofloxacin-based regimens.
Bangladesh short course – treatment outcomes

**TABLE 5. OUTCOME OF TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS GROUPED BY REGIMEN CATEGORY, BANGLADESH DAMIEN FOUNDATION PROJECTS**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Regimens 1+2</th>
<th>Regimen 3</th>
<th>Regimen 4</th>
<th>Regimen 5</th>
<th>Regimen 6</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Col %</td>
<td>n</td>
<td>Col %</td>
<td>n</td>
<td>Col %</td>
</tr>
<tr>
<td>Completion*</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Cure</td>
<td>71</td>
<td>68.9</td>
<td>20</td>
<td>57.1</td>
<td>30</td>
<td>66.7</td>
</tr>
<tr>
<td>Death</td>
<td>11</td>
<td>10.7</td>
<td>5</td>
<td>14.3</td>
<td>4</td>
<td>8.9</td>
</tr>
<tr>
<td>Default</td>
<td>15</td>
<td>14.6</td>
<td>7</td>
<td>20.0</td>
<td>4</td>
<td>8.9</td>
</tr>
<tr>
<td>Failure</td>
<td>6</td>
<td>5.8</td>
<td>3</td>
<td>8.6</td>
<td>6</td>
<td>13.3</td>
</tr>
<tr>
<td>Relapse</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Not fitting any of the above*</td>
<td>103</td>
<td>100.0</td>
<td>35</td>
<td>100.0</td>
<td>45</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Definition of abbreviation:** Col % = column percent.

* Treatment completion is reported only for the gatifloxacin-treated cohort because cure criteria could not always be met due to the short regimen and incomplete post-treatment follow-up. However, all had converted, one patient with two and one with three negative cultures during treatment (and before moving away), and the others all had at least four negative cultures.

* One patient failed clinically but not according to the bacteriological criteria, and the treatment was changed to a salvage regimen. Although all cultures preceding the event were negative, this patient would not fit the analysis criteria. In the final analysis on effectiveness and survival, this patient was counted as an adverse outcome.
Cameroon Short Course MDR TB Regimen

- Prospective observational study of MDR-TB
- Patients treated with a standardized 12-month regimen
  - including gatifloxacin, clofazimine, prothionamide, ethambutol and pyrazinamide throughout,
  - Supplemented by kanamycin and isoniazid during an intensive phase of a minimum of 4 months
- No prior 2nd line TB drug exposure (> 1 mo)
- Treatment success ~ 90%
  - a single failure
  - no relapses

Cameroon Short Course MDR TB Regimen

Table 1  Anti-tuberculosis drug dosages by body weight in kilogrammes

<table>
<thead>
<tr>
<th>Drug</th>
<th>&lt;40</th>
<th>40-54</th>
<th>55-70</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatifloxacin, mg</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Pyrazinamide, mg</td>
<td>800</td>
<td>1200</td>
<td>1600</td>
<td>2000</td>
</tr>
<tr>
<td>Ethambutol, mg</td>
<td>600</td>
<td>800</td>
<td>1200</td>
<td>1400</td>
</tr>
<tr>
<td>Isoniazid, mg</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Prothionamide, mg</td>
<td>500</td>
<td>500</td>
<td>750</td>
<td>1000</td>
</tr>
<tr>
<td>Clofazimine, mg</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Kanamycin, mg/kg</td>
<td>15-20</td>
<td>15-20</td>
<td>15-20</td>
<td>15-20</td>
</tr>
</tbody>
</table>

Notes:
- INH and gatifloxacin doses more standardized
- **All MTB strains susceptible to FQ and kanamycin
- 120 pts (80%) had failed on previous treatment; no prior 2nd line drug exposure (> 1 mo)
- 30 pts (20%) were HIV (+)
Cameroon Short Course MDR TB Regimen - outcomes

Notes:
- Of the 150 patients, 132 met the definition of cure and 2 completed treatment
- 134 (89.3%, 95%CI 84.5–94.4) had a ‘successful treatment outcome’, with no relapses
- HIV (+) had no significant impact in outcomes
Niger MDR TB Short course trials

• 65 patients evaluated:
  • 12-months: high doses of gatifloxacin, clofazimine, ethambutol and pyrazinamide throughout
  • Supplemented with kanamycin, prothionamide and INH (med-high dosing) during intensive phase (min. of 4 mo.)

• Drug resistance identified:
  • EMB (n=45, 69.2%), ofloxacin (n=1, 1.5%), ETH (n = 7, 10.8%)
  • 64 pts with patients had strains with medium- to high-level INH resistance

• All MTB strains susceptible to kanamycin; all but 1 susceptible to FQ/Oflox

• “Cure” in 58 patients (89.2%, 95%CI 81.7–96.7), 6 died and 1 defaulted.

WHO Statement – short course regimens

• Short course (9-12 mo) extended combination therapy may be considered for Rif-R and MDR-TB patients who:
  • Have NOT previously been treated with 2nd-line drugs
  • Resistance to FQs and injectables has been excluded (or considered highly unlikely)
  • Adults and children
  • HIV positive or negative

• No recommendation on short course regiments for extrapulmonary DR TB disease
WHO Statement – short course regimens

• WHO recommends AGAINST short course regimens in pts who
  
  • Received previous 2nd line drug therapy for > 1 mo
  • Documented or likely drug resistance to medications in the regimen
    • Esp the FQs and/or Injectables

• Controversial use during pregnancy
  • Ethionamide/prothionamide and Inj agents are teratogenic
The role of surgical resection

• Favorable results reported with resectional lung surgery in patients with MDR-TB

• Resective surgery considered for:
  • Patients with high-grade drug resistance (limited drug options)
  • Relatively localized lung disease
  • Lack of initial response

• NJMC, Denver with high experience
  • Dedicated surgeon / surgical team (Dr. M Pomeranz)
  • Pneumonectomy or lobectomy

Pomerantz et al. J of Thorac Cardiovasc Surg. 2001;121(3) 448-53
The role of surgical resection - timing

• When surgical resection is favored
  • e.g. cavitary disease, necrotic / avascular lung tissue

• Optimal timing for surgery can be difficult to determine

• Consider delaying surgery for a few months after start of combination drug therapy
  • Lower TB organism burden
  • Enhanced patient nutrition / weight gain
  • Improved postoperative tissue healing

Pomerantz et al. J of Thorac Cardiovasc Surg. 2001;121(3) 448-53
Successful MDR-TB outcomes not dependent on surgical resection

- Medical therapy “usually” successful – via:

• Inclusion of better 2\textsuperscript{nd} / 3\textsuperscript{rd} line drugs - e.g.:
  • Newer fluoroquinolones (Moxifloxacin / levofloxacin); Injectables (improved dosing approaches); Linezolid
  • Availability of Bedaquiline and delamanid
  • A bonus when PZA or EMB remain active

• Medical management a consideration when an active combination initial drug regimen can be composed
  • Inclusion of $\geq$ 5 drugs with in vitro activity

• Pushing serum levels to upper limits of therapeutic window (roles for TDM)

Principles for MDR and XDR-TB management

• Providers *need to be comfortable* asking for assistance
  • Most providers are not overly experienced in drug-resistant TB management
  • Our Mayo TB Center practice utilizes Region-5 MDR-TB Team consensus with more complex TB drug-resistant cases
  • Such patients may not have a “2nd chance” for treatment success
Principles for MDR and XDR-TB management - II

Public health departments need to be involved for case management:

• Directly observed therapy (DOT) *is crucial*
• Heightened monitoring for treatment response and drug toxicities
• Contact investigations
Clinical case anecdote

My first patient as a new Mayo Clinic Staff

July 2000
Case Presentation: 33 yo Somali Woman

- 10/99 Abnormal CXR for LTBI screen – no follow-up
- 5/00 – Diagnosis with pulmonary tuberculosis
  RUL cavitary and multifocal disease
  - AFB smear and mycobacteria cultures both (+)
    - DST pending
  - Minimal cough
  - HIV negative (-); immunocompetent
- 7 months pregnant
Case Presentation – TB and pregnant:

- 5/12/00 started on INH/RIF/EMB
  - PZA avoided (in USA) during pregnancy
    - Lack of data during pregnancy to determine safety
    - PZA still used during pregnancy for following:
      - HIV (+) patient
      - Suspected drug-resistance
      - WHO (non-USA) recommendations (PZA given during pregnancy outside of USA)
- Patient with some improvement over 1 month
- Then susceptibility results……..
## Case Presentation – MDR TB

### Susceptibility data from Mayo:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
<th>Drug</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>&gt; 0.1 Resistant</td>
<td>Kanamycin</td>
<td>8 Sensitive</td>
</tr>
<tr>
<td>Rifampin</td>
<td>&gt; 2 Resistant</td>
<td>Capreomycin</td>
<td>8 Sensitive</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>&gt; 100 Resistant</td>
<td>Ethionamide</td>
<td>4 Sensitive</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>&lt; 2.5 Sensitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>&gt; 2 Resistant</td>
<td></td>
<td></td>
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</tbody>
</table>

### Additional susceptibility data from NJH:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
<th>Drug</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&lt; 2 Sensitive</td>
<td>PAS</td>
<td>8 Sensitive</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&lt; 2.0 Sensitive</td>
<td>Cycloserine</td>
<td>60 Sensitive</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>&lt; 2.0 Sensitive</td>
<td>Linezolid</td>
<td>&lt; 4.0 Sensitive</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>&lt; 2.0 Sensitive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dr. J Wilson joins staff here……………Takes over patient care
Case Presentation: 33 yo Somali Woman

- MDR TB case

- What else?
  - 7 months pregnant
  - Husband with prior TB and abnormal CXR
  - 4 young children at home

CXR
Case Presentation – MDR TB

→ all things considered – this could have been worse!!

Susceptibility data from Mayo:

- Isoniazid: > 0.1 Resistant
- Rifampin: > 2 Resistant
- Pyrazinamide: > 100 Resistant
- Ethambutol: < 2.5 Sensitive
- Streptomycin: > 2 Resistant

- Kanamycin: 8 Sensitive
- Capreomycin: 8 Sensitive
- Ethionamide: 4 Sensitive

Additional susceptibility data from NJH:

- Amikacin: < 2 Sensitive
- Levofloxacin: < 2.0 Sensitive
- Gatifloxacin: < 2.0 Sensitive
- Ofloxacin: < 2.0 Sensitive

- PAS: 8 Sensitive
- Cycloserine: 60 Sensitive
- Linezolid: < 4.0 Sensitive

Dr. J Wilson joins staff here……………Takes over patient care
Case Presentation – 33 yo Somali woman with MDR TB; 8 mo. pregnant

• Consultation with NJMC & MDH:
  • Medications stopped late/end May 2000 (Combination second-line MTB drug therapy delayed until after delivery of baby).
  • Newborn baby immediately separated from mother until mid 8/00 when pt. was Smear & culture negative)
  • Controversial – other treatment approaches can be very appropriate

• Late June, 2000, started: Ethambutol; IV Amikacin; Levofloxacin; Ethionamide; Cycloserine (B6)
  • Before wide usage of LZD, Moxi
Case Presentation – MDR TB

**Amikacin** – aminoglycosides can produce *irreversible* CN8 toxicity

- Audio toxicity: AMK, KAN
- Vestibular toxicity: SM
**Case Presentation – MDR TB**

**Ethambutol** – optic neuritis; red-green color discrimination and visual acuity

- Edema of optic disc
- Mild temporal pallor
Case Presentation – MDR TB

- Stopped ethambutol
- Continued levofloxacin, ethionamide, cycloserine and PAS
- Later re-developed severe GI distress

Question: Which is most likely drug?
Case Presentation – MDR TB

- GI distress – N/V, upset stomach, ache

Common with most TB drugs (early in therapy) but most problematic with **ethionamide**

- GI upset also common with PAS
Drug Resistant TB: General Treatment principles

• Poly-resistant MTB disease
  • Use as many 1\textsuperscript{st}-line agents as possible, plus a fluoroquinolone and (in some cases) an injectable agent (e.g. aminoglycoside)

• MDR-TB disease
  • Use a minimum of 4 or more drugs to which the MTB is susceptible (at least 3 drugs not used previously with in vitro activity, including injectable)
    • Begin with available 1\textsuperscript{st}-line TB drugs
    • Add a fluoroquinolone (Moxi > Levo > Cipro)
    • Add injectable agent (AMK/Kana/SM/Capreo)

• XDR-TB – include above principles
  • May need to include 3\textsuperscript{rd}-line drug (in vitro activity but limited clinical experience) – includes:
    Clofazimine
    Linezolid
    Amox/Clavulanate
    Imipenem
    Macrolides
    High-dose INH
• Drug resistant TB can be challenging to manage
• Some things in life seem very ‘unnatural’
• But if a basset hound can actually run……then together we can eliminate drug resistant TB!

The End

Questions?
Pearls of Select 2nd-line TB Drugs
Aminoglycoside – associated Ototoxicity

Consider:
- Monthly audiology testing
- Monthly office-based vestibular testing

Note – CN8 toxicity is irreversible
GI Intolerance: Nausea/Vomiting

Especially common with:

- Ethionamide
- PAS
- Clofazimine
- **Any start-up program with many pills**
Endocrine problems:

Including:

- Hypothyroidism
- Hypoglycemia
- Other (esp. with ETA)
  - Gynecomastia, hair loss, menstrual irregularity

Especially common with:

- Ethionamide
- PAS
Dose Escalation Strategies: Ethionamide, Cycloserine, PAS

• Relevant Drugs:
  • Ethionamide
  • Cycloserine
  • Para-aminosalicylic acid

• Purpose:
  • Improved patient tolerance (gradual dose escalation)
  • More precise dosing for acceptable serum drug levels
Dose Escalation Strategies: Ethionamide, Cycloserine, PAS

- Ethionamide & cycloserine
  - Start with 250 mg daily x a few days
  - Increase to 250 mg bid x a few days
    - Check serum level
  - Increase to 250 mg/qAM and 500 mg q/PM

- PAS (Paser granules, sachet packets)
  - Start with 2 gm bid x a few days
  - Increase to 2 gm/qAM and 4 gm qPM x few days
  - Increase to 4 gm bid
    - Check serum level

Target dosing
Linezolid usage

• An oxazolidinone

• Toxicities – significant (> 50%) and include:
  • Neuropathies - peripheral & optic
  • Myelosuppression
  • Hyperlactatemia
  • Risk of serotonin syndrome with SSRIs

• Bacteriostatic; binds rRNA; inhibits protein synthesis

• Dosing: 600 mg daily successfully used

Linezolid usage

- Dosing of 300 mg /d can be effective for MDR-TB
  - Possibly lower adverse effects compared to 600 mg daily or bid
- 300 mg/d dosing can achieve serum concentrations greater than MIC values (<0.25 mg/L)
- Favorable penetration into pulmonary & soft tissues

Bedaquiline (Situro) – a new diarylquinoline

- Inhibits mycobacterial ATP synthase
- Spectrum of activity includes: *M. tuberculosis* and select NTM (including MAC)
- Indications: treatment of pulmonary MDR-TB in pts ≥ 18 yo when optimal TB drug program cannot be constructed
- BDQ dosing: 400 mg daily x 2 weeks, then 200 mg TIW x 22 weeks – then off

CDC RTMCC meeting January 14-15, 2013
Bedaquiline – concerns and limitations

- Increased risk of death (11.4% vs. 2.5% in comparator group)
- Elevated QTc (although not felt to be a major risk by CDC group meeting)
  - May be additive with other QTc prolonging drugs - *caution by FDA
- Higher hepatic adverse reactions
- Drug interactions via Hepatic CYP 3A
  - M2 is major metabolite (4-6x less potent)
  - BDQ does not increase or decrease 3A4 activity
  - Rifampin will decrease BDQ levels (via accelerated 3A4 metabolism)
- Limited data in HIV co-infected patients

CDC RTMCC meeting January 14-15, 2013
New drugs on the horizon

- OPC – 67683 (Delamanid)
  - Nitro dihydro imidazoxoazole
- PA-824; nitroimidazole
  - Combinations with PZA and moxifloxacin
- AZD 5847; oxazolidinone
Remember – the negative stigma of drug-resistant TB is not simply abroad