Treatment of Drug Resistant TB

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Objectives
- Definition of other drug resistant (ODR), multiple drug resistant (MDR TB) and extensive drug resistant TB (XDR TB)
- Discussion of the drugs and therapies used for treatment of drug resistant TB
- Discussion of isolation issues related to MDR TB
- Case discussion of MDR TB

Definition of DR TB
- **MDR TB**
  - A specimen of *M. tuberculosis* isolate that is resistant to at least INH and RIF
  - Can be resistant to other drugs as well
- **ODR TB**
  - Resistant to INH, sensitive to RIF, with or without resistance to other first or second-line drugs
  - Resistant to RIF, sensitive to INH, with or without resistance to other drugs
  - Resistance to any (1 or more) first-line drugs (EMB, PZA, SMN) other than INH or RIF

Revised Definition XDR TB (10/06)
- Resistance to at least INH and RIF from among the 1st-line anti-TB drugs (MDR TB)
- **Plus** resistance to any fluoroquinolone,
- **And** to at least one of 3 injectable 2nd-line anti-TB drugs used in TB treatment
  - Capreomycin
  - Kanamycin
  - Amikacin
Tuberculosis Cases and Rates
New York City, 1980 – 2009*

760 Cases in 2009

Year

Case Rate

Number of Cases Rate/100,000

*Multi-drug resistant TB* defined as resistant to at least INH & RIF

Tuberculosis Drug Resistance
New York City, 1992-2009

MDRTB: resistance to at least INH & RIF

ODRTB: resistance to other first-line drugs but not multi-drug resistant

Multidrug Resistant TB* by HIV Status
New York City, 1992-2009

% of MDR Cases

*Defined as resistant to at least INH & RIF*
Characteristics of MDR Cases (N=8) New York City, 2009

- 100% are non-US born
- 13% are HIV-positive
- 100% had pulmonary TB only
- 75% reside in Queens
- 86% of those eligible are on DOT

Drug-Resistant TB

- Drug-resistant TB transmitted same way as drug-susceptible TB
- Drug resistance is divided into two types
  - Primary resistance develops in persons initially infected with resistant organisms
    - Health-care associated transmission
    - Community transmission
  - Secondary resistance (acquired resistance) develops during TB therapy
    - Nonadherence to therapy
    - Inappropriate therapy

Rates of Natural Resistance in *M. tuberculosis*

- Isoniazid 1 in $10^5$
- Rifampin 1 in $10^8$
- Ethambutol 1 in $10^5$
- Streptomycin 1 in $10^5$
- INH & RIF 1 in $10^{14}$

Number of organisms in a TB cavity = $10^6$-$10^{14}$
Emergence of Resistance
(Inappropriate Therapy)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>6/08</th>
<th>9/08</th>
<th>2/09</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Ethambutol</td>
<td></td>
<td></td>
<td>I</td>
</tr>
</tbody>
</table>

- Smear: + + +
- Culture: + + +

Susceptibility

| Isoniazid | R | R | R |
| Rifampin  | S | R | R |
| Ethambutol| S | S | R |

DOT?

MDR/ODR TB

- Patients with DR TB need to have
  - Accurate and prompt identification
  - Notification to the field staff and provider(s)
  - Appropriate case management
## Antituberculosis Drugs

**First-Line Drugs**
- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Rifabutin*
- Rifapentine

**Second-Line Drugs**
- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin
- Capreomycin
- Levofloxacin*
- Moxifloxacin*

* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB

## Third-Line Drugs Used in MDR TB Treatment

### Linezolid
- Used since 2000 in selected cases
- Adverse effects of pancytopenia and peripheral/optic neuritis
  - may or may not be reversible
  - may or may not be ameliorated by vitamin B₆
- Consider using 600 mg daily
- Use with caution with selective serotonin reuptake inhibitors (SSRIs)

## Third-Line Drugs Used in MDR TB Treatment—II

- Clofazimine
  - More commonly used in patients with leprosy
  - Used in selected cases
  - Needs IND
- γ-Interferon
  - Research medication
  - Inhaled
  - Used only with pulmonary disease
  - AFB smear +
  - Expensive

### Step 1

Begin with any 1st-line agents to which the isolate is susceptible.

Add a fluoroquinolone and an injectable drug based on susceptibilities.

- Pyrazinamide
- Ethambutol
- Levofloxacin
- Moxifloxacin

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

Adapted from: Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, available from Francis J. Curry National Tuberculosis Center
Principles for Managing MDR TB

- MDR TB should never be treated without expert consultation of a specialist in MDR TB treatment.
- Patients must be treated with a regimen of at least 3-6 anti-TB medications to which the strain is likely to be susceptible (4-6 or better).

Principles for Managing MDR TB - 2

- A single new drug should never be added to a failing regimen.
- When initiating or revising therapy, always attempt to use at least 3 previously unused drugs to which there is in vitro susceptibility:
  - One agent should be an injectable agent.
  - A good response does not justify continuation of an inadequate regimen.
Principles for Managing MDR TB - 3

- Patients with DR TB should be treated under a program of DOT
  - Intermittent regimens should not be used. All 2nd-line agents must be administered daily
  - Twice/day DOT should be used when feasible, and more frequent dosing than twice daily should be avoided
  - All doses must be observed for the patient to get credit

Principles for Managing MDR TB – 4

- Injectable agents can be given 5 days/wk initially. After culture conversion, dosing for injectable can be 2-3 times/wk
- With extensive disease or slow conversion of sputum cultures, the injectable should be used for longer periods after culture conversion
- Fluoroquinolones:
  - Levofloxacin is the preferred agent of choice in adults
  - Moxifloxacin is used with the approval of the BTBC Bureau Director

Principles for Managing MDR TB - 5

- Resistance to RIF is generally associated with cross-resistance to rifabutin and rifapentine
  - When RIF resistance is present but \textit{in vitro} sensitivity to rifabutin is reported, treatment should be the same as if RIF-resistant
- There is cross-resistance between amikacin and kanamycin
- Determination of resistance to PZA is problematic, but is uncommon in the absence of resistance to other 1st-line drugs
  - If monoresistance to PZA is found, consider the specimen may be \textit{M. bovis}, not \textit{M. tb}

Principles for Managing MDR TB - 6

- Serum drug level monitoring may be used
- Most medications used to treat MDR TB are known to cause fetal abnormalities or have not been studied adequately regarding their safety in pregnancy
  - In pregnant MDR TB patients, PZA can be used as a main agent, and is recommended by WHO & ATS
  - WHO recommends its use in pregnancy even for drug-susceptible TB patients
  - In the U.S., it is considered a category C agent
Principles for Managing MDR TB - 7

- Some experts use EMB at a dose of 25 mg/kg daily when used as treatment of patients with MDR TB
  - If this higher dose is used, monthly visual monitoring is recommended.
  - If isolates show resistance to INH only at a low concentration, INH 900 BIW (high intermittent dose) can be used.
  - Do not rely on its effectiveness as a main agent. This may be applicable to the W strain.
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment.

Principles for Managing MDR TB - 8

- For all with RIF resistance (mono-RIF or MDR TB), consider extended therapy if:
  - There is cavitary or extensive disease.
  - The patient is HIV-positive or has risk factors for HIV infection.
  - The patient is immunosuppressed.
  - Time to culture conversion is prolonged.
- All patients with RIF-resistant TB should be followed for at least 12-24 months after treatment completion.

Drug Intolerance

- In general, length of treatment for drug intolerance is the same as for drug resistance.

INH Resistant TB

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation Phase</th>
<th>Total length</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF/PZA/EMB</td>
<td>RIF/PZA/EMB</td>
<td>6-9 months</td>
</tr>
<tr>
<td>If extensive</td>
<td>Extend to 9 months</td>
<td></td>
</tr>
<tr>
<td>disease</td>
<td>if culture</td>
<td></td>
</tr>
<tr>
<td>consider</td>
<td>positive at 2</td>
<td></td>
</tr>
<tr>
<td>adding a 4th</td>
<td>months</td>
<td></td>
</tr>
<tr>
<td>agent (FQ or</td>
<td>Preferred regimen,</td>
<td></td>
</tr>
<tr>
<td>IA)</td>
<td>even in pregnancy</td>
<td></td>
</tr>
<tr>
<td>RIF/PZA/EMB</td>
<td>RIF/EMB</td>
<td>9 months</td>
</tr>
<tr>
<td>2 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIF/EMB + FQ</td>
<td>RIF/EMB + FQ</td>
<td>12 months</td>
</tr>
<tr>
<td>or IA</td>
<td>or IA</td>
<td></td>
</tr>
<tr>
<td>2 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Rifampin Resistant TB

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation Phase</th>
<th>Total Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH/PZA/ EMB Injectable+FQ</td>
<td>2-3 months after culture conversion</td>
<td>18 months (preferred regimen)</td>
</tr>
<tr>
<td>INH/PZA/ SMN + EMB</td>
<td>2-3 months after culture conversion</td>
<td>9 months</td>
</tr>
</tbody>
</table>

### PZA+ Strep Resistance

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation Phase</th>
<th>Total Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH/RIF/EMB</td>
<td>2 months</td>
<td>9 months</td>
</tr>
</tbody>
</table>

### INH/EMB ± SMN Resistant TB

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation Phase</th>
<th>Total Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF/PZA/FQ ± injectable</td>
<td>2-3 months after culture conversion</td>
<td>9-12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months after culture conversion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>whichever longer</td>
</tr>
</tbody>
</table>

### MDR TB

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation</th>
<th>Total Length</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH/RIF ± SMN</td>
<td>PZA/FQ plus</td>
<td>6 months</td>
<td>Extend</td>
</tr>
<tr>
<td></td>
<td>1-2 second</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>line agents*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH/RIF/FQ</td>
<td>PZA/FQ plus</td>
<td></td>
<td>Cavitory</td>
</tr>
<tr>
<td></td>
<td>1-2 second</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>line agents*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH/RIF/PZA</td>
<td>EMB/FQ plus</td>
<td></td>
<td>HIV positive</td>
</tr>
<tr>
<td></td>
<td>1-2 second</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>line agents*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH/RIF/PZA</td>
<td>FQIA 5 days</td>
<td></td>
<td>Immune suppressed</td>
</tr>
<tr>
<td></td>
<td>a week plus</td>
<td></td>
<td>Prolonged</td>
</tr>
<tr>
<td></td>
<td>2-3 second</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>line agents*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>at least 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 second</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>line agents*</td>
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MDR TB

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<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation</th>
<th>Total length</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH/RIF/EMB/SMN/kan/ETH/RRB + PZA (strain W and W variants)</td>
<td>FQ plus at least 2-3 other agents to which the organism is susceptible</td>
<td>6 months after culture conversion</td>
</tr>
<tr>
<td>INH/RIF/EMB/SMN/FQ / + 2nd line IA +PZA (i.e. XDR TB)</td>
<td>Any 3-4 drugs to which organism is susceptible. Consider Linezolid, Clofazamine &amp; γ-interferon</td>
<td>Until culture conversion</td>
</tr>
</tbody>
</table>

General Side Effects of Medications

- All medications can cause skin rash
- Allergic reactions/hypersensitivity
- Diarrhea

Drug Activity Against TB

Bactericidal:
- INH
- Rifampin
- Streptomycin
- Capreomycin
- Kanamycin/Amikacin
- Moxifloxacin

Bacteriostatic:
- PZA
- Ethambutol
- Levofloxacin (may be bactericidal)
- Ethionamide
- PAS
- Cycloserine

Treatment of Contacts to Drug Resistant TB

- Persons exposed to INH-resistant TB:
  - Rifampin:
    - 4 months adults
    - 6 months children

- Persons likely infected with MDR TB:
  - 6-12 months PZA and EMB, or PZA and FQ (i.e., ≥ 2 drugs to which organism is susceptible)
  - Usually 12 months for immunocompromised and children
  - Option to follow for 2 years if no treatment given
**Indications for Surgery**

- Adequate 1st and 2nd-line regimens of anti-TB medications have failed to cure or cause *M. tb* cultures to convert to negative within 4 to 6 months
- Sufficient medications are available to treat the patient postoperatively
- Localized disease
- Remaining lung tissue is relatively free of disease
- Acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection
- Additional possible indications for surgery:
  - Major bronchial obstruction
  - Severe hemoptysis, or
  - Bronchopleural fistula (BPF)

**Surgery for MDR TB Patients**

- Even after lung resection, the patient must complete a full course of treatment (i.e., 18-24 months after culture conversion) with medications to which the *M.tb* strain is susceptible
- If patient is culture negative after surgery, then surgery is considered the conversion episode

**Infection Control Issues Related to Multidrug Resistant TB Patients**

- MDR TB patients should remain hospitalized or on home isolation if an outpatient until:
  - 3 sputum smears are AFB-negative
  - Clinically improved and near resolution of cough
  - Tolerating an appropriate treatment regimen
  - Patient agrees to DOT and it has been arranged
  - Proper arrangements have been made for follow-up
  - A home assessment should be done with evaluation for insertion of a HEPA filter in the residence

**Situations Where Culture Conversion Should Be Confirmed Prior to Return to Work**

- Work sites where individuals with drug-susceptible TB and MDR TB should be excluded until culture conversion is confirmed:
  - Work sites where persons with HIV or other immunocompromised patients are cared for
  - Neonatal intensive care units
  - Patient care areas
  - Nursing homes
  - Congregate settings such as daycare and schools
Returning MDR TB Patients to Work or School-Culture Conversion

- MDR TB patients should be kept from returning to work or school, or transferring to another congregate setting such as a shelter or nursing home until culture conversion is confirmed
  - 2 consecutive negative cultures at least 2 weeks apart
- Culture conversion is necessary unless the patient will be transferred to an airborne infection isolation room in the congregate setting
- Exceptions can be made for certain types of work settings, if all the conditions in previous slide are met
  - Decided in consultation w/ Office of Medical Affairs

Follow-up of MDR TB Patients after Treatment Completion

- Patients with TB resistant to INH and RIF or treated without RIF/RBT
  - Medical evaluation every 4 months during the 1st year after treatment completion
  - Then every 6 months during the 2nd year
- Months: 4, 8, 12, 18, 24 post treatment
- Educate about relapse and to return if they develop symptoms

Case #1

- The DR Coordinator informs you that your patient at the private doctor’s office has INH resistant tuberculosis. The patient has a cavity in the RUL, and still has positive cultures into the 2nd month of therapy
  1. What are the different options for treatment, and the length of therapy?
  2. Who should be informed?
  3. How should the patient’s 4 year old and 10 year old children be treated for LTBI?

Case #2

- Patient in the clinic is still infectious after 1 ½ months of INH/RIF/PZA/EMB. The report comes back from the lab that the patient is resistant to INH/RIF/PZA and sensitive to EMB
  1. How should this patient be treated initially and for how long?
  2. When can the patient return to work/school?
  3. What should be discussed in the case management meeting about this patient?
  4. How long should the patient be followed after completing therapy 18 months later?