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 Drug Resistant 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 1\textsuperscript{st} -line anti-TB drugs (MDR TB)
- Plus resistance to any fluoroquinolone,
- And to at least one of 3 injectable 2\textsuperscript{nd}-line anti-TB drugs used in TB treatment
  - Capreomycin
  - Kanamycin
  - Amikacin
WHO: MDR-TB among new TB cases, 1994 - 2009

MAP Distribution of proportion of MDR-TB among new TB cases, 1994–2009

- Green: 0–<3
- Light Green: 3–<6
- Yellow: 6–<12
- Orange: 12–<18
- Red: ≥18
- White: No data available
- Gray: Subnational data only

* Australia, Democratic Republic of the Congo, Fiji, Guam, New Caledonia, Solomon Islands and Qatar reported data on combined new and previously treated cases.
Tuberculosis Cases and Rates
New York City, 1980 – 2009*

760 Cases

*Rates since 2000 are based on 2000 Census data
Primary MDR TB
United States, 1993–2009*

*Updated as of July 1, 2010.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
Multi-drug Resistant TB*
New York City, 1992-2009

*Multi-drug resistant TB or MDRTB: organism resistant to at least INH & RIF
Tuberculosis Drug Resistance
New York City, 1992-2009

% of all Cx+ cases with susceptibility results who had drug resistance

Year

MDRTB: resistance to at least INH & RIF
ODRTB: resistance to other first-line drugs but not multi-drug resistant
Multi-drug Resistant Tuberculosis* by HIV Status
New York City, 1992-2009

% of MDR Cases

<table>
<thead>
<tr>
<th>Year</th>
<th>92</th>
<th>93</th>
<th>94</th>
<th>95</th>
<th>96</th>
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</tr>
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</table>

*Defined as resistant to at least INH & RIF
Characteristics of MDR Cases (N=9)  
New York City, 2009

- 100% are non-US born
- 11% are HIV-positive
- 100% had pulmonary TB only
- 100% 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
    - Nosocomial 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 $10^6$
- Rifampin 1 in $10^8$
- Ethambutol 1 in $10^6$
- Streptomycin 1 in $10^5$
- INH & RIF 1 in $10^{14}$

Number of organisms in a TB cavity = $10^9$-$10^{11}$
Pathogenesis of Drug Resistance I
Pathogenesis of Drug Resistance II
## Emergence of Resistance

(Inappropriate Therapy)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>6/09</th>
<th>9/09</th>
<th>2/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
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<tr>
<td>Rifampin</td>
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<tr>
<td>Ethambutol</td>
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</tr>
</tbody>
</table>

| Smear       | + | + | + |
| Culture     | + | + | + |

### Susceptibility

| Isoniazid | R | R | R |
| Rifampin  | S | R | R |
| Ethambutol| S | S | R |
Emergence of Resistance (Nonadherence and Inappropriate Therapy)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>6/08</th>
<th>9/08</th>
<th>12/08</th>
<th>3/09</th>
<th>6/09</th>
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<tbody>
<tr>
<td>Isoniazid</td>
<td></td>
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<tr>
<td>Rifampin</td>
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<tr>
<td>Ethambutol</td>
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</tr>
<tr>
<td>Smear</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Culture</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
</tr>
</tbody>
</table>

Susceptibility:

- **Isoniazid**: S R R R R
- **Rifampin**: S S S R R
- **Ethambutol**: S S R R

DOT indicated by question mark.
MDR and ODR TB

- Patients with DR TB need to have
  - Accurate and prompt identification
  - Notification to the field staff and provider(s)
  - Appropriate case management
  - Appropriate treatment based on drug susceptibility test results
# Antituberculosis Drugs

<table>
<thead>
<tr>
<th>First-Line Drugs</th>
<th>Second-Line Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Cycloserine</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>p-Aminosalicylic acid</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>Rifabutin*</td>
<td>Amikacin or kanamycin*</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Capreomycin</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin*</td>
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<tr>
<td></td>
<td>Moxifloxacin*</td>
</tr>
</tbody>
</table>

* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB
Drug Activity Against TB
Bacteriocidal vs. Bacteriostatic

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

**Bacteriostatic**
- PZA
- Ethambutol
- Levofloxacin (may be bactericidal)
- Ethionamide
- PAS
- Cycloserine
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 Investigational New Device (IND) from FDA

- **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

**First-line drugs**

- Pyrazinamide
- Ethambutol

**Fluoroquinolones**

- Levofloxacin
- Moxifloxacin

**Injectable agents**

- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

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Adapted from *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*, available from Francis J. Curry National Tuberculosis Center
Step 1

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

Add a fluoroquinolone and an injectable drug based on susceptibilities

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

- **Fluoroquinolones**
  - Levofloxacin
  - Moxifloxacin

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

PLUS

One of these

PLUS

One of these

Step 2

Pick one or more of these

- **Oral second-line drugs**
  - Cycloserine
  - Ethionamide
  - PAS

Adapted from *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*, available from Francis J. Curry National Tuberculosis Center
Step 1

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

Add a fluoroquinolone and an injectable drug based on susceptibilities.

First-line drugs
- Pyrazinamide
- Ethambutol

Fluoroquinolones
- Levofloxacin
- Moxifloxacin

Injectable agents
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

PLUS
One of these

Step 2

Add 2nd-line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously).

Oral second-line drugs
- Cycloserine
- Ethionamide
- PAS

Step 3

If there are not 4-6 drugs available consider 3rd-line in consult with MDRTB experts.

Third-line drugs
- Imipenem
- Linezolid
- Macrolides
- Amoxicillin/Clavulanate
- Clofazimine
- High-dose isoniazid

Consider use of these in consult with MDRTB experts.

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 3-5 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 \textit{in vitro} susceptibility
  - One agent should be an injectable agent
  - A good response does not justify continuation of an inadequate regimen
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 (IA) can be given 5 days/wk initially
  - After culture conversion, dosing can be 2-3x/wk
- With extensive disease or slow conversion of sputum cultures, the IA should be used for longer periods after culture conversion
- Capreomycycin is the initial IA of choice
- Surgery should be considered if a patient’s cultures fail to convert to negative after 4 months of appropriate treatment
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

Fluoroquinolones:
  • Oral agents, well tolerated
  • One of the two most important agents in MDR treatment
  • Levofloxacin is the preferred agent of choice in adults
Specific Drug Resistances

- 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
- 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 *M. bovis*, not *M. tb*
Rifampin Resistance

- 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

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
MDR TB in Pregnancy

- Most medications used to treat MDR TB are known to cause fetal abnormalities or have not been studied adequately regarding their safety in pregnancy.

- 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.
Monitoring Serum Drug Levels

Serum drug level monitoring can be used in patients with the following medical conditions:

- HIV positive/AIDS
- Diabetes
- Malabsorption syndromes
- Renal failure
- Failure to improve on treatment/relapse
- MDR TB
Drug Intolerance

- In general, length of treatment for drug intolerance is the same as for drug resistance.
Drug Regimens for Resistant TB
<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation Phase</th>
<th>Total length</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RIF/PZA/EMB</strong></td>
<td><strong>RIF/PZA/EMB</strong></td>
<td><strong>6-9 months</strong></td>
</tr>
</tbody>
</table>
| If extensive disease consider adding a 4th agent (FQ or IA) | 2 months | • Extend to 9 months if culture positive at 2 months
| | 9 months | • Preferred regimen, even in pregnancy |
| **RIF/PZA/EMB** | **RIF/EMB**       | **9 months** |
| 2 months | | |
| **RIF/EMB + FQ or IA** | **RIF/EMB + FQ or IA** | **12 months** |
| 2 months | | |
# 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>INH/PZA/ EMB + FQ</td>
<td>18 months (preferred regimen)</td>
</tr>
<tr>
<td>2-3 months after culture conversion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH/PZA/ SMN + EMB</td>
<td>INH/PZA/ SMN + EMB</td>
<td>9 months</td>
</tr>
<tr>
<td>2-3 months after culture conversion</td>
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</tbody>
</table>
# PZA+ Strep Resistance

<table>
<thead>
<tr>
<th></th>
<th>Initial Phase</th>
<th>Continuation Phase</th>
<th>Total length</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INH/RIF/EMB</strong></td>
<td>2 months</td>
<td><strong>INH/RIF</strong></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><strong>RIF/PZA/FQ + injectable</strong></td>
<td>2-3 months after culture conversion</td>
<td><strong>RIF/PZA/FQ</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td>Resistance</td>
<td>Initial Phase</td>
<td>Continuation</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>INH/RIF + SMN</td>
<td>PZA/EMB/FQ &amp; IA, 5 days a week</td>
<td>PZA/EMB/FQ</td>
</tr>
<tr>
<td>INH/RIF/EMB + SMN</td>
<td>PZA/FQ/IA, 5 days a week plus at least 1-2 second-line agents*</td>
<td>PZA/FQ, plus at least 1-2 second-line agents</td>
</tr>
<tr>
<td>INH/RIF/PZA + SMN</td>
<td>EMB/FQ/IA, 5 days a week plus at least 1-2 second-line agents*</td>
<td>EMB/FQ, plus at least 1-2 second-line agents</td>
</tr>
<tr>
<td>INH/RIF/PZA/EMB + SMN</td>
<td>FQ/IA, 5 days a week plus at least 2-3 second-line agents*</td>
<td>FQ, plus at least 2-3 second-line agents</td>
</tr>
</tbody>
</table>

Initial Phase:

- 6 months after culture conversion

Continuation:

- Extend therapy:
  - Cavitary disease
  - HIV positive or risk factors
  - Immuno-suppressed
  - Prolonged time to culture conversion

*Second-line agents may include any of the following: kanamycin, capreomycin, amikacin, ethionamide, cycloserine, pyrazinamide, linezolid, delamanid, or others as determined by susceptibility testing.
# MDR TB

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Initial Phase</th>
<th>Continuation</th>
<th>Total length</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INH/RIF/EMB/SMN/KAN/ETH/RBT + PZA</strong> (strain W and W variants)</td>
<td><strong>FQ/IA</strong> plus at least 2-3 other agents to which the organism is susceptible</td>
<td>6 months after culture conversion</td>
<td>18-24 months after culture conversion</td>
</tr>
</tbody>
</table>
| **INH/RIF/EMB/SMN/FQ/+ 2nd-line IA +PZA** (i.e. XDR TB) | Any 3-4 drugs to which organism is susceptible. Consider Linezolid, Clofazamine & γ-interferon | Until culture conversion | Any 3-4 drugs to which organism is susceptible. Consider Linezolid, Clofazamine & γ-interferon | At least 24 months after culture conversion  
• Ideal therapy duration unknown  
• Evaluate for early surgery |
Indications for Surgery

- Adequate 1\textsuperscript{st} and 2\textsuperscript{nd} -line regimens of anti-TB medications have failed to cure or cause 
  \textit{M. tb} cultures to convert to negative within 4 to 6 months
- Sufficient medications are available to treat the patient postoperatively
- Disease is sufficiently localized to allow lobectomy or pneumonectomy
- Remaining lung tissue is relatively free of disease
- Acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection
Indications for Surgery II

Additional possible indications for surgery:

- Major bronchial obstruction
- Severe hemoptysis
- 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.
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)
    - Limited experience with FQ as single agent
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?