Disclosure / Disclaimer

• No financial conflicts of interest

• Mention of off-label use of FDA-approved medications
Objectives

Treatment of TB and Drug Resistance of TB

• Describe the current guidelines for the treatment of TB disease including the newly released CDC guidelines

• Identify the basic principles of drug resistant TB
XDR-TB

Photojournalist James Nachtwey - TED Prize wish come true

37 photographs in 3 minutes

Millions of lives saved: XDR TB

https://www.youtube.com/watch?v=yj8KZNI6-W8
TUBERCULOSIS also known as TB

CDC Tuberculosis (TB) Transmission and Pathogenesis Video

https://www.youtube.com/watch?v=9112brXCOVc
Risk associated with development of active TB disease
Case

- 54 year old African American male, US born
- Seen at Emergency Department with complaints of productive cough, discolored, non-bloody, worse at night
- Associated with fevers, chills, SOB
- Last 5 months – Not feeling well and lost 30 pounds

Past Medical History
- COPD
- Hepatitis C
- Alcoholism
- Pneumonia - 6 months prior

Social History
- Homeless - ? Street
  - Sister, shelter, jail/prison
- Smokes ½ PPD
- Alcohol abuse: drinks daily ~ 40oz beer/day
- No illicit drug use
Radiologic Findings (1)

CXR

RUL irregular consolidation
Radiologic Findings (2)

CT

RUL cavitary lesion
RLL consolidation
Hospital course

- Admitted negative air isolation unit
- TST = reactive ?mm
- QuantiFERON-TB Test: positive
- AFB sputum smear: positive
- Nucleic Acid Amplification Test: positive
- Started on 4 drug anti-TB therapy
Active TB Disease

**Pulmonary**
- Lungs

**Extrapulmonary**
- Lymphatic system
- Kidney
- Central nervous system
- Bones (Potts)
- Disseminated (miliary TB)
Eggs & milk
Fresh air & Sunshine
Rest & Exercise

Treatment
Antimyobacterial Drugs

First-Line Drugs

- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)
2\textsuperscript{ND} AND 3\textsuperscript{RD} LINE TB DRUGS

- **2\textsuperscript{ND} LINE**
  - **Injectables**: Amikacin, capreomycin, kanamycin, (streptomycin)
  - **Fluoroquinolones**: Moxifloxacin, levofloxacin
  - Ethionamide, prothionamide, cycloserine, PAS, terizodone

- **3\textsuperscript{rd} LINE**
  - Bedaquiline
  - Delamanid
  - Linezolid
  - Clofazamine
  - Meropenem
  - High dose INH
  - Amoxicillin clavulanate
Bedaquiline Sirturo, December 28, 2012
US FDA approved
MDR-TB and XDR-TB
Third-Line Drugs Used in MDR TB Treatment -2

• Clofazimine
  • More commonly used in patients with leprosy
  • Used in selected cases
  • Needs Investigational New Device (IND) from FDA

• Bedaquiline
  • 1\textsuperscript{st} new class of TB medication approved since RIF
  • New class of antibiotics, diarylquinolones
  • Given as part of MDR combination therapy
  • New mechanism of action: inhibits ATP synthase
Linezolid

• Oxazolidinone
  • Bacteriostatic; binds rRNA; inhibit protein synthesis
• Since 2000- selected cases, recently a 2\textsuperscript{nd} or 3\textsuperscript{rd} line drug
• Adverse effects:
  • \textit{Pancytopenia and peripheral/optic neuritis}
    • May or may not be reversible
    • May or may not be ameliorated by vitamin B\textsubscript{6}
  • Risk of serotonin syndrome with selective serotonin reuptake inhibitors (SSRIs)- use with caution
  • Lactic acidosis
• Consider using 600 mg daily (300mg/day being studied)

Lee et al., NEJM 2012;367


http://cid.oxfordjournals.org/content/early/2016/07/20/cid.ciw376.full.pdf+html
Basic TB Treatment Regimen

INITIAL (INTENSIVE) PHASE

4 drugs X 8 weeks

CONTINUATION PHASE

- Isoniazid + Rifampin
- 18 weeks

Isoniazid
Rifampin
Pyrazinamide
*Ethambutol*
CDC Guidelines 2016

**Intensive Phase** 8 weeks

- Daily dosing, rather than intermittent dosing, is preferred.
- If intermittent therapy is needed, use treatment three times per week for patients with:
  - Low risk of relapse (i.e. drug-susceptible TB organisms, non-cavitary and/or smear negative) and
  - Negative HIV-infection test result
2 month sputum very important

**INITIAL (INTENSIVE) PHASE**
- 4 drugs X 8 weeks

**CONTINUATION PHASE**
- Isoniazid + Rifampin
- 18 weeks

Isoniazid
Rifampin
Pyrazinamide
*Ethambutol*
CDC Guidelines 2016

Continuation Phase 18 weeks

- Daily dosing is recommended.
- If intermittent therapy is needed, treatment three times per week is preferred.
Why Extend Continuation-Phase Treatment for 3 more Months?

- Cavitary disease and positive sputum culture at 2 months of treatment, is associated with increased relapse in clinical trials
- Extended continuation phase decreased relapses in silicotuberculosis (from 20% to 3%)
**Bacteriology**

<table>
<thead>
<tr>
<th>Sputum Specimen</th>
<th>AFB Smear</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital day 1</td>
<td>Positive 2+</td>
<td><em>M. tuberculosis</em></td>
</tr>
<tr>
<td>Hospital day 2</td>
<td>Positive 3+</td>
<td><em>M. tuberculosis</em></td>
</tr>
<tr>
<td>Hospital day 6</td>
<td>Positive 3+</td>
<td><em>M. tuberculosis</em></td>
</tr>
<tr>
<td>Hospital day 11</td>
<td>Positive 2+</td>
<td></td>
</tr>
<tr>
<td>Hospital day 20</td>
<td>Positive 2+</td>
<td></td>
</tr>
</tbody>
</table>

**Drug Susceptibility Test**

<table>
<thead>
<tr>
<th>Method</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid Culture</td>
<td>7 – 21 days</td>
</tr>
<tr>
<td>Solid Culture</td>
<td>3 – 8 weeks</td>
</tr>
</tbody>
</table>

*Mayo Clinic Center for Tuberculosis*
MDR TB (Multidrug Resistant)

- *M. tuberculosis* isolate that is **resistant** to at least **INH and RIF**
- Can be resistant to other drugs as well
ODR TB (Other drug resistant)

- Resistant to **INH**, sensitive to RIF, with or without resistance to other first or second-line drugs

  OR

- Resistant to **RIF**, sensitive to INH, with or without resistance to other drugs

  OR

- Resistance to any (1 or more) first-line drugs (**EMB, PZA, SMN**) other than INH or RIF
XDR TB (Extensively drug resistant)

- 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
GenExpert Assay Procedure for the MTB/RIF Test.

1. Sputum liquefaction and inactivation with 2:1 sample reagent
2. Transfer of 2 ml material into test cartridge
3. Cartridge inserted into MTB-RIF test platform (end of hands-on work)
4. Sample automatically filtered and washed
5. Ultrasonic lysis of filter-captured organisms to release DNA
6. DNA molecules mixed with dry PCR reagents
7. Seminested real-time amplification and detection in integrated reaction tube
8. Printable test result

Time to result, 1 hour 45 minutes

<table>
<thead>
<tr>
<th>Locus (region) examined*</th>
<th>Result</th>
<th>Interpretation (based on in-house evaluation of 550 clinical isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rpoB (RRDR)</td>
<td>Mutation: TOG&gt;TGG; Ser531Trip</td>
<td>Rifampin resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are RMP-R.)</td>
</tr>
<tr>
<td>inhA (promoter)</td>
<td>Mutation: C-15T</td>
<td>Isoniazid resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with these mutations are INH-R.)</td>
</tr>
<tr>
<td>katG (ser315 codon)</td>
<td>Mutation: AGC&gt;ACC; Ser315Thr</td>
<td>Likely Ethambutol Resistant (67% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are EMB-R.)</td>
</tr>
<tr>
<td>embB (Met306,Gly406)</td>
<td>Mutation: ATG&gt;ATA; Met306Ile</td>
<td>Likely PZA resistant.</td>
</tr>
<tr>
<td>pncA (promoter, coding region)</td>
<td>Mutation: TGG&gt;CGG; Trp88Arg</td>
<td>Cannot rule out fluoroquinolone resistance. (80% of FQ-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)</td>
</tr>
<tr>
<td>gyrA (QRDR)</td>
<td>No mutation</td>
<td>Cannot rule out resistance to injectable drugs (kanamycin, capreomycin, am</td>
</tr>
<tr>
<td>rrs (1400 region)</td>
<td>No mutation</td>
<td>• 91% of AMK-R isolates have a mutation in the rrs locus;</td>
</tr>
<tr>
<td>eis (promoter)</td>
<td>No mutation</td>
<td>• 87% of KAN-R isolates have a mutation in either the rrs locus or the eis</td>
</tr>
<tr>
<td>tlyA (entire ORF)</td>
<td>No mutation</td>
<td>• 55% of CAP-R isolates have a mutation in either the rrs locus or the tly/</td>
</tr>
</tbody>
</table>

*A negative results (e.g., no mutation) does not rule out contributory mutations present elsewhere in the genome.

MDDR assays were developed and the performance characteristics determined by the DTBE Reference Labora.
Factors to be considered in deciding to initiate treatment empirically for active tuberculosis (TB) (prior to microbiologic confirmation).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Elevated concern for adverse treatment events (eg, severe liver disease, pregnancy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 2 years</td>
<td>No TB exposure risk</td>
</tr>
<tr>
<td>TB exposure risk (eg, contact, born in higher TB incidence country)</td>
<td></td>
</tr>
</tbody>
</table>

| Laboratory/Radiographic | 
|-------------------------|-------------------------|
| Radiographic imaging consistent with TB | Radiographic imaging not consistent with TB |
| Evidence of Mtb infection (ie, positive TST or IGRA) | |
| Extended time to microbiologic confirmation (eg, Rapid molecular test not available) | |
| Pathologic findings consistent with TB | |
| AFB smear positive, Rapid molecular test positive | AFB smear positive, Rapid molecular test negative |
| AFB smear negative, Rapid molecular test positive | AFB smear negative, Rapid molecular test negative |

| Clinical Status/Suspicion | 
|---------------------------|---------------------------|
| Life-threatening disease | Clinically stable |
| Symptoms typical for TB | Symptoms not typical for TB |
| Alternative diagnosis less likely | Alternative diagnosis |

| Public Health | 
|----------------|----------------|
| Concern for loss to follow-up | Low transmission risk |
| High transmission risk (eg, congregate setting, corrections) | |


Favors Delayed or No Treatment
Empirical MDR treatment vs Individualized Regimen??

• Deferring treatment until drug-susceptibility results are available is an appropriate option only if the patient is not severely ill and can be isolated to prevent infection of contacts.
## Treatment Strategies

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standardized treatment</strong></td>
<td>Regimen is designed based on Drug Resistance Surveillance (DRS) data from a representative patient population</td>
</tr>
<tr>
<td><strong>Empirical treatment</strong></td>
<td>Regimen is individually designed based on patient’s previous history of TB treatment and DRS data as above</td>
</tr>
<tr>
<td><strong>Individualized treatment</strong></td>
<td>Regimen is designed based on the patient’s previous history of TB treatment and individual DST results</td>
</tr>
</tbody>
</table>
**Step 1**

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

Add a fluoroquinolone and an injectable drug based on susceptibilities

<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>Streptomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kanamycin</td>
</tr>
</tbody>
</table>

Adapted from *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed.*, available from Curry International 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

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

**Adapted from Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed., available from Curry International 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

Step 2

Pick one or more of these

Oral second-line drugs
- Cycloserine
- Ethionamide
- PAS

Step 3

Consider use of these

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

Adapted from Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed., available from Curry International 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 3-5 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 *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

- Injectable agents 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 injectable should be used for longer periods after culture conversion
- Streptomycin resistance may accompany INH resistance
- 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 - 4

• 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
Specific Drug Resistances

• If isolates show resistance to INH only at a low concentration, High intermittent dose can be used
  • Do not rely on its effectiveness as a main agent
• 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 mono resistance 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 *in vitro* sensitivity to rifabutin is reported, treatment should still be the same as if RIF-resistant

• For all with RIF-resistance (mono-RIF or MDR TB), consider extended therapy (up to 18-24 months) 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
Treatment of HIV-related MDR-TB

• Rapid diagnosis of drug resistance
• Important to treat with the most active anti-TB regimen available
• Initiate antiretroviral therapy based on CD$_4$ count and other individual patient variables
• Use therapeutic drug monitoring when drug interactions are possible or malabsorption is suspected
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

OK to use: INH, RIF, EMB, PZA, PAS, Cycloserine
Do not use: FQ, Aminoglycoside, Ethionamide
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 patients with drug intolerance is the same as for those who have drug resistance
Indications for Surgery - 1

- 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 - 2

- Additional possible indications for surgery:
  - Major bronchial obstruction
  - Severe hemoptysis
  - Bronchopleural fistula (BPF)

- 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
Directly Observed Therapy (DOT)

- Health care worker watches patient swallow each dose
- DOT is preferred management strategy for all patients
- Can reduce acquired drug resistance, treatment failure, and relapse
- Nearly all regimens can be intermittent if given as DOT
- DOT reduces total number of doses and encounters
- For drug-resistant TB, use daily regimen and DOT
Directly Observed Therapy (DOT)
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 FQ and EMB, or PZA and EMB
    (i.e., ≥ 2 drugs to which organism is susceptible)
  • Limited experience with FQ as single agent
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
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
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 a 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
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
Question #1: Define MDR- TB

A. Resistance to INH, RIF, PZA and EMB
B. Resistance to RIF
C. Resistance to INH and RIF
D. Resistance to EMB and PZA
Question #2:

True or False:

Continuation phase should be extended if culture is still positive at 2 months in a patient with cavitary TB lung disease

A. True
Acknowledgements

- S Mase, MD
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- Ben Franklin TB Control