Disclosures

• No financial disclosures or conflicts of interest
Regional Resources

Mayo Clinic Center for Tuberculosis provides support for 11 states in Region 5:

- Illinois
- Indiana
- Iowa
- Michigan
- Minnesota
- Montana
- North Dakota
- Ohio
- South Dakota
- Wisconsin
- Wyoming

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Objectives

• Know the nomenclature for drug-resistant tuberculosis cases
• Know the risk factors for TB drug resistance
• Understand the basics of TB drug resistance testing
• Review the principles for treatment of drug-resistant TB
• Appreciate the challenges in treating drug-resistant TB
TB Drug Resistance

• Understand when it might be an issue
Nomenclature

• **Mono-resistant TB**
  • Resistance to 1 first-line TB drug only

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

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

• **Extensively Drug Resistant (XDR) TB**
  • MDR (isoniazid & rifampin) + plus:
  • Resistance to a fluoroquinolone + plus:
  • Resistance to an injectable (kanamycin, streptomycin, amikacin)
TB Resistance = Challenges

• Difficult to treat
  • More drug intolerances and adverse effects

• Longer duration of therapy
  • Depends on resistance pattern

• More expensive treatment

• Different recommendations for isolation
  • For MDR and XDR TB

• Traditional latent TB infection (LTBI) treatment doesn’t work
Risk Factors for Drug-resistant TB

1. Previous TB therapy – especially with
   • Prior non-DOT based therapy
   • Patient non-adherence
   • Incomplete treatment, lack of documentation
   • Non-CDC, non-WHO endorsed standard regimens

2. Contact with a patient with drug-resistant TB

Seaworth B. IDCNA Vol 16, No. 1, 73-105. March 2002
Risk Factors for Drug-resistant TB

3. Persons from countries with higher rates of drug-resistant/MDR TB cases

Risk Factors for Drug-resistant TB

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

5. International TB endemic regions:
   - Prolonged hospitalization (TB endemic regions)
   - HIV co-infection (TB endemic regions)
   - Lack of sustainable drug availability to patients

6. Overuse of fluoroquinolones in other infection/syndromes (Respiratory infections, UTI)

7. Delays in diagnosing TB (inappropriate antibiotic exposure)

Global Epidemiology

• Among **new** TB cases, 3.3% are MDR
• Among **retreated** cases, 20% are MDR

Epidemiology in US - 2015

• 88 cases of MDR TB
• MDR TB accounted for
  • 0.4% of culture-confirmed cases among US-born persons
  • 1.2% of cases among foreign-born persons
• 72 of the 88 (82%) cases occurred in patients with no reported history of prior TB disease treatment
• 1 case of XDR

Case 1:

• You are consulted about a 22 year female patient with no past medical history (HIV-negative) who immigrated to the US one year ago from Russia. Her CXR was normal at the time of immigration. She has no prior history of LTBI or TB disease and no prior history of TB treatment. She reports 1 month of cough. CXR shows 4 cm complex right upper lobe cavitary lesion. Sputum is AFB positive, MTB PCR is positive, and *rpoB* mutation is detected, indicating rifampin resistance. The patient is clinically stable and lives with her husband at home.
Case 1 continued:

What do you recommend next?

A. This patient has rifampin monoresistant-TB. She should be started immediately on isoniazid, pyrazinamide, and ethambutol.

B. This patient has rifampin monoresistant-TB. She should be started immediately on isoniazid, pyrazinamide, ethambutol, and a fluoroquinolone.

C. More information is needed prior to starting the patient on therapy. Send the TB isolate for molecular detection of drug resistance (MDDR) testing MDDR at the CDC, and hold off on starting TB therapy. MDR-TB is a consideration in this case.
Case 1 continued:

What do you recommend next?

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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 \(~96\%\) 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-base drug susceptibility testing (DST) is still required
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
Molecular detection of drug resistance (MDDR) 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>

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
Case 1 Continued

The MDDR testing on your patient comes back with mutations in *rpoB* (predicting rifampin resistance) and *inhA* (predicting isoniazid resistance). No other mutations are detected on MDDR testing. Phenotypic drug susceptibility results are pending. What do you do next?
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
Mono resistance – 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)
**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 1st line drug, then add FQ and injectable (amikacin/kanamycin/SM/capreomycin)
- Add oral 2nd line drugs to compose 4-6 drug regimen
- If there are not 4-6 active drugs available, then consider 3rd line drugs (BDQ, clofazimine, carbapenem/clavulanate, high dose-INH)
- Surgery can be considered with complex cavitary disease or slow clinical response
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

**Use any available**

**PLUS**

**One of these**

**PLUS**

**One of these**

**First-line drugs**

- Pyrazinamide
- Ethambutol

**Fluoroquinolones**

- Levofloxacin
- Moxifloxacin

**Injectable agents**

- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

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.

### Third-line drugs

<table>
<thead>
<tr>
<th>Bedaquiline</th>
<th>Meropenem/Clavulanate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delamanid</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
Back to Case 1: MDDR -> RIF and INH resistance

- You begin the patient on a treatment regimen of ethambutol, pyrazinamide, moxifloxacin, amikacin, and linezolid though DOT
- Phenotypic drug susceptibility testing demonstrates resistance to isoniazid and rifampin and sensitivity to all second line drugs that were tested
- What else might you consider in management of this case?
When to start therapy?

- 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
Additional Considerations for MDR-TB

• 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)

• Therapeutic drug monitoring is recommended
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
Principles for MDR and XDR-TB management

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
Additional Considerations for MDR-TB

• “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
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

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**
Successful MDR-TB outcomes not dependent on surgical resection
- Medical therapy “usually” successful – via:

- Inclusion of better 2nd / 3rd 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 ≥ 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
We never got past case 1…

• You are asked when your 22 yo female patient with MDR-TB can come off respiratory isolation (home isolation) and return to work…

Your answer is:

• A) When she has evidence of clinical improvement & 3 negative sputum AFB smears

• B) When she has evidence of clinical improvement & 1 negative MTB PCR from sputum

• C) When she has evidence of clinical improvement & 2 negative sputum cultures
We never got past case 1…

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- **B)** When she has evidence of clinical improvement & 1 negative MTB PCR from sputum
- **C)** When she has evidence of clinical improvement & 2 negative sputum cultures
Pearls of Select 2nd-line TB Drugs
Case 2:

33 yo Somali female, HIV-negative, with cavitary, pulmonary TB and the following MTB phenotypic susceptibilities
Case Presentation – MDR TB

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
Case 2:

Patient is started on Ethambutol; IV Amikacin; Levofloxacin; Ethionamide; Cycloserine (B6)

Three months later she develops hypothyroidism.
Case 2:

Which drug is the most likely cause of the hypothyroidism?

A. Ethambutol
B. Amikacin
C. Levofloxacin
D. Ethionamide
E. Cycloserine
Case 2:

Which drug is the most likely cause of the hypothyroidism?

A. Ethambutol
B. Amikacin
C. Levofloxacin
D. Ethionamide
E. Cycloserine
Endocrine problems:

Including:

- Hypothyroidism
- Hypoglycemia
- Other
  - Gynecomastia, hair loss, menstrual irregularity
- Ethionamide
- PAS
- Both Ethionamide and PAS require sTSH monitoring – additive effect when used in combination.
Case 2:

- Started on levothyroxine – continued ethionamide
- But then, 5 months into treatment – developed asymptomatic high-frequency hearing loss.

**Question: Which drug is most suspect?**

A. Ethambutol
B. Amikacin
C. Levofloxacin
D. Ethionamide
E. Cycloserine
Case 2:

Question: Which drug is most suspect?

A. Ethambutol
B. Amikacin
C. Levofloxacin
D. Ethionamide
E. Cycloserine
Aminoglycoside – associated Ototoxicity

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

Note – CN8 toxicity is irreversible
Case 2:

- Amikacin stopped
- Para-aminosalicylic acid (PAS) granules started
- 6 months into treatment – patient developed mild visual disturbance (decreased acuity):

**Question:** Which is the most suspect drug?

A. Ethambutol  
B. PAS  
C. Levofloxacin  
D. Ethionamide  
E. Cycloserine
Case 2:

Question: Which is the most suspect drug?

A. Ethambutol
B. PAS
C. Levofloxacin
D. Ethionamide
E. Cycloserine
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
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
Linezolid

- An oxazolidinone

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

- Dosing: 600 mg daily successfully used

- May be able to use 300 mg/day, depending on weight and if there is toxicity at 600 mg/day
  - can achieve serum concentrations greater than MIC values (≤0.25 mg/L)

Take Home Points

• Rifampin resistance should be considered a marker of MDR-TB, until proven otherwise

• Molecular drug detection of drug resistance (MDDR) can provide information on probable drug resistance, while phenotypic susceptibilities are pending
  • Not all mutations are known, so not all resistance can be predicted
Take Home Points

• MDR-TB is defined by resistance to both isoniazid and rifampin

• MDR-TB treatment regimen:
  • 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)
Public Health is the Key to Controlling TB
Drug Resistance and ending TB

whitaker.jennifer@mayo.edu
Bedaquiline (Situro) – a new diarylquinoline

- Inhibits mycobacterial ATP synthase
- Spectrum of activity includes: \textit{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
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