MDR Care = team sport
Drug-Resistant TB: Definitions

- **Mono-resistant**: Resistance to a single drug
- **Poly-resistant**: Resistance to more than one drug, but not the combination of isoniazid and rifampicin
- **Multidrug-resistant (MDR)**: Resistance to at least isoniazid and rifampicin
- **Extensively drug-resistant (XDR)**: MDR plus resistance to fluoroquinolones and at least 1 of the 3 injectable drugs (amikacin, kanamycin, capreomycin)
Drug resistant TB in US

What’s the likelihood of caring for a case in your clinic?
Primary MDR TB, United States, 1993 – 2013

Number of cases

- 95 total cases MDR (82 cases primary) in 2013
- 92% of primary MDR were foreign-born
- 4 cases of XDR (range 0-10 per year)
Primary Anti-TB Drug Resistance, United States, 1993 – 2013*

- INH resistant: 8.9%
- MDR-TB resistance: 1%
Case scenario

when should we suspect drug-resistance?
Case 1
Case: Gisela Schecter, MD

- 21-year-old Filipina woman with Type I DM recently emigrated from the Philippines
- No TB screening at the time of immigration
- History of treatment for TB with INH +/- RIF as a child and, more recently, with INH, RIF, PZA and EMB given by SAT last year
- Presented with cough x 5 months, progressive SOB/DOE x 6 weeks, pleuritic chest pain and fever to 101 degrees
Case 1

Case: Gisela Schecter, MD
Case 1

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Case 1

Case: Gisela Schecter, MD

- 21-year-old Filipina woman with Type I DM recently emigrated from the Philippines

- No TB screening at the time of immigration

Where are the high risk areas in the world?

- History of treatment for TB with INH +/- RIF as a child and, more recently, with INH, RIF, PZA and EMB given by SAT last year

- Presented with cough x 5 months, progressive SOB/DOE x 6 weeks, pleuritic chest pain and fever to 101 degrees
MDR cases among notified TB cases
WHO report 2014

MDR-TB cases estimated to occur among notified pulmonary TB cases, 2013
Estimated global incidence and proportion of MDR among TB cases 2013

Estimated:

- 480,000 new cases of MDR
- 3.5% of all new cases and 20.5% of previously treated cases have MDR
- Of notified cases - more than half are from India, China, and the Russian Federation
- Proportion of previously treated cases with MDR up to 50-69% in some countries (Azerbaijan, Belarus, Estonia, Kyrgyzstan, Republic of Moldova, Tajikistan, Uzbekistan)

WHO 2014 report
100 countries had reported at least one XDR-TB case by 2013 (survey data estimate 9.0% of MDR have XDR)
“Biological Fitness” of the *Mtb* organism is not generally worsened by resistance

- Studies have shown robust growth among RIF resistant and MDR strains

- Once created, drug resistant TB can spread to other people

- The majority of global MDR TB (>70%) is among new patients (i.e. was transmitted and not acquired)
Case 1

Case: Gisela Schecter, MD

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Drug-Resistant Tuberculosis

MDR-TB is a manmade problem… It is costly, deadly, debilitating and is a major threat to our current control strategies.
Random Naturally Occurring Resistance in Bacterial Population

- INH = 1 in $10^6$
- RIF = 1 in $10^8$
- EMB = 1 in $10^6$
- Strep = 1 in $10^6$

INH and RIF = $10^6 \times 10^8 = 1$ in $10^{14}$
patient-related factors

provider-related factors

program-related factors
Recognition of risk factors:

- **Foreign-born from countries or ethnicities with high prevalence of MDR**
  - Ex. Hmong refugees, Tibetan ancestry
  - Former USSR, China, Korea, Peru, Honduras are disproportionately MDR

- **History of prior therapy** (most powerful predictor) or failing current 1\textsuperscript{st}-line rx

- **Known contact to DR case**

- Presence of RIF resistance predicts MDR

- HIV+ (higher incidence of RIF mono-resistance)
High-risk MDR: Action Steps

- Obtain **rapid molecular test for drug sensitivity**
  - GenXpert RIF/Mtb (RIF only)
  - WA state: DRSS [INH \((katG, inhA)\); RIF\((rpoB)\); PZA \((pncA)\)]
  - CA state: Pyrosequencing [INH \((katG, inhA)\); RIF\((rpoB)\); FQ \((gyrA)\); Injectables \((rrs)\)]
  - CDC Molecular Detection of Drug Resistance (MDDR) program (above drugs plus ethambutol)
  - Others: HAIN line-probe, MODS

- Order both **first/second-line conventional DST**

- Consider initiation of **expanded regimen**
Genes Associated with Resistance

- **RIF** resistance
  - *rpoB* core region (> 95%)
- **INH** resistance
  - *katG, inhA* (85%)
  - *ahpC, ndh, and unknown* (10-15%)
- FQ resistance
  - *gyrA* (>90%)
- Injectable resistance
  - *rrs* (70-90%)
Case 1

- Started on a four drug standard regimen plus moxifloxacin 400 mg po qd x1 week (is this wise?)
- Three sputum specimens for AFB smear were positive and the sediment was sent for molecular beacon (MB) testing
- MBs found mutations conferring both INH + Rifampin resistance
What would you do next?

1. Wait for phenotypic DST’s for first and second line drugs
2. Continue RIPE and moxifloxacin
3. Begin an empiric MDR-TB regimen
After MDR-TB service consultation, the patient was placed on:

- Amikacin 870 mg IV five times weekly
- Moxifloxacin 400 mg po qd
- Cycloserine 500 mg po qd
- PAS 4 gm po bid
- EMB 15 mg/kg po qd
- PZA 25 mg/kg
- Vitamin B6 50 mg
Case 1

- Susceptibility results show **resistance to all first-line drugs**
- Quinolones:
  - CDC: Res: Oflox, Cipro
  - MDL: Borderline (2.0) Res: Levo
  - NJM: Intermediate (1.0) Res: Moxi
- Was there a mechanism for acquired fluoroquinolone resistance?
- Role for continuing moxifloxacin?
- Treatment regimen?
Clinically did well and smear-converted

- EMB, PZA, discontinued
- Moxifloxacin increased to 600 mg qd
- Linezolid 600 mg qd added
- Repeat CXR
Case 1: Gisela Schecter, MD

[Image of a chest X-ray]
MDR-TB Treatment Principles

- Perform thorough patient evaluation prior to starting treatment
- Never add a single drug to a failing regimen
- Aim for 4-6 likely effective drugs (susceptible and/or no prior use) in the intensive phase
- Initially, one drug should be bactericidal injectable agent (amikacin, kanamycin, capreomycin)
- Later generation fluoroquinolone should be used whenever possible
<table>
<thead>
<tr>
<th>Drug</th>
<th>Cross Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH, specifically low level resistance (<em>InhA</em>)</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>RIF</td>
<td>All rifamycins*</td>
</tr>
<tr>
<td>PZA</td>
<td>None</td>
</tr>
<tr>
<td>EMB</td>
<td>None</td>
</tr>
</tbody>
</table>

* There might be some exceptions for rifabutin
## Cross-resistance for Second-line Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cross Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>None</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Possibly amikacin</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Kanamycin*</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>All fluoroquinolones**</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>None</td>
</tr>
<tr>
<td>PAS</td>
<td>None</td>
</tr>
<tr>
<td>Linezolid</td>
<td>None</td>
</tr>
</tbody>
</table>

*Some Km mutations w/o cross-resistance to Am

** Some exceptions with moxifloxacin
MDR-TB Treatment Principles

- Continue injectable for at least 6 months post-culture conversion (Intensive phase)
- Continue at least 3 oral drugs for total treatment duration of 20 months (18 months post-culture conversion)
- When possible do not limit continuation phase regimen to 3 drugs, especially if extensive disease/resistance
- Use daily, not intermittent therapy (some exceptions: renal, later injectables, HD INH)
- MDR & XDR-TB ➔ seek expert consultation
Curry International Tuberculosis Center
1-877-390-NOTB  or  1-877-390-6682
www.currytbcenter.ucsf.edu
# Building a Regimen 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

<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>
Building a Regimen for MDR-TB

**STEP 2**
If 4 drugs are not identified in Step 1: Add second-line drugs until you have 4-6 drugs to which the isolate is susceptible (and preferably which have not been used to treat the patient previously)

Pick one or more of these

<table>
<thead>
<tr>
<th>Oral second-line drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycloserine</td>
</tr>
<tr>
<td>Ethionamide</td>
</tr>
<tr>
<td>PAS</td>
</tr>
</tbody>
</table>

(Linezolid)
If there are not 4-6 drugs available in the above categories, consider third-line drugs in consultation with an expert.

<table>
<thead>
<tr>
<th>Third-line drugs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>Meropenem</td>
</tr>
<tr>
<td>Bedqualine</td>
<td>Amoxicillin/Clavulanate</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Imipenem/cilastin</td>
<td>High-dose INH</td>
</tr>
</tbody>
</table>
Linezolid (Zyvox)

- Increasing experience
- Has been found to be well tolerated and a good adjunctive medication when other drugs unavailable*
- Excellent activity against *M. tb in vitro*
- Dose – 600 mg po qd (case series using 300mg daily)
- Cost of therapy – high
- Side effects – myelosuppression, peripheral neuropathy, optic neuropathy
- Avoid tyramine containing foods, soy products, SSRIs, tricyclic antidepressants and OTC meds containing pseudoephedrine and phenylpropanolamine → serotonin syndrome

*Linezolid: A Promising New Agent for Multi-Drug Resistant Tuberculosis Treatment
P. Hadjiangelis, E. Leibert, T.J. Harkin, W.N. Rom, R. Condos. Division of Pulmonary and Critical Care Medicine, NYU School of Medicine/Bellevue Chest Service, NY, NY
Regimens for XDR-TB

- In the face of quinolone and injectable drug resistance, treatment choices are limited.
- Linezolid and any remaining injectable become the mainstay of treatment, along with whatever oral medications are left to which there is *in vitro* susceptibility.
- Surgery if disease is localized.
- Consider Bedaqualine.
- Some patients may not be treatable.
Global Drug Pipeline: Recently Approved

Diacon AH, et al. NEJM 2009;360:2397
Gler MT, et al. NEJM 2012;366:2151
Bedaquiline (Janssen)

- **Class** – diarylquinoline
- **Mechanism of action** - novel ATP synthase inhibitor

**Activity**
- **In vitro** – bactericidal (replicating and dormant)
- **Animal** – bactericidal and sterilizing activity
- **Early bactericidal activity** similar to isoniazid or rifampicin
Bedaquiline (TMC207) for MDR-TB

- Phase 2, randomized, controlled trial
- 47 patients with MDR-TB randomized to TMC207 or placebo plus standard five-drug regimen

**Results**
- Reduced time to conversion
- Increased proportion that converted (48% vs 9%)
- Mild to moderate AEs with nausea more common with TMC207 (26% vs 4%)

Diacon AH, et al. NEJM 2009;360:2397
## Mortality in Bedaquiline: Phase II Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Bedaquine: No.</th>
<th>Bedaquine: (%)</th>
<th>Control: No.</th>
<th>Control: (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C202</td>
<td>Randomized, open-label, dose ranging EBA study</td>
<td>2/45</td>
<td>4.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C208 (Stage 1)</td>
<td>Double-blind, randomized, placebo-controlled superiority trial</td>
<td>2/23</td>
<td>8.7</td>
<td>2/24</td>
<td>8.3</td>
</tr>
<tr>
<td>C208 (Stage 2)</td>
<td>Double-blind, randomized, placebo-controlled superiority trial</td>
<td>10/79</td>
<td>12.6</td>
<td>4/81</td>
<td>4.9</td>
</tr>
<tr>
<td>C209</td>
<td>Noncomparative, single-arm open label trial</td>
<td>16/233</td>
<td>6.9</td>
<td>No control</td>
<td>No control</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>30/380</td>
<td><strong>7.9</strong></td>
<td>6/205</td>
<td><strong>2.9</strong></td>
</tr>
</tbody>
</table>

Black box warning increase risk of death

CDC MMWR 2013;62;1-12
CDC Provisional Guidelines for Use of Bedaquiline (Sirturo)

- When an effective treatment regimen cannot be provided:
  - Bdq may be used for 24 weeks of treatment in adults with laboratory-confirmed pulmonary MDR-TB
  - Bdq may be used on a case-by-case basis in children, HIV infected persons, pregnant women, extrapulmonary MDR-TB, and patients with comorbid conditions
  - Bdq may be used on a case-by-case basis for durations longer than 24 weeks (5.5 mo. ½ life)

- DOSE: 400 mg once daily for 2 weeks, then 200 mg three times a week for 22 weeks, taken with food

CDC MMWR 2013;62;1-12
CDC Provisional Guidelines: Bedaquiline

- No dose adjustment with mild/mod renal impairment
- Drug interactions – metabolized through CYP3A
- Hepatotoxicity
  - AST, ALT, bilirubin, alkaline phosphatase monthly
- Cardiac toxicity
  - Baseline ECG and then 2, 12, and 24 weeks
  - Baseline K, Ca, Mg levels
  - Discontinue if QTcF >500 ms or ventricular arrhythmias
Updated MDR Guidelines

- The WHO 2011 Guidelines were based on the results of a meta-analysis that included 32 studies and >9000 patients (XDR-TB patients were excluded)
- WHO is updating
- New ATS/CDC/IDSA MDR guideline underway
- New DR-TB Survival Guide later 2015 (!)
WHO 2011 Recommendations

- Four second-line drugs likely to be effective (including a parenteral agent) as well as PZA, should be used in the intensive phase (conditional recommendation/very low quality of evidence).

- Regimens should include at least PZA, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide) and either cycloserine or PAS, if cycloserine cannot be used (conditional recommendation/very low quality of evidence).
Duration of Therapy Recommended

WHO 2011 Recommendations:

- An intensive phase of at least 8 months’ duration is recommended (conditional recommendation, very low quality of evidence)
  - Adjusted relative risk for cure peaked at intensive phase 7.1-8.5 mo.

- A total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment (conditional recommendation, very low quality of evidence)
  - Adjusted relative risk of cure peaked at 18.8-21.5 mo
  - Peaked later if prior therapy at 27.6-30.5 mo.
Short course “Bangladesh” regimen

Nine (to twelve) month MDR regimen:

- 4 mo: Kanamycin/gatifloxacin/prothionimide/high-dose INH/clofazamine/ethambutol/PZA; then 5 mo: gatifloxacin/clofazamine/ethambutol/PZA

- 2005-2011: Treatment success 84.5% (n=515); 

- Ongoing multi-country observational study

- Separate STREAM trial [randomized 9 mo (except uses Moxi) vs “standardized” regimen]; adds BDQ arm (6 and 9 month regimens)
Patient-centered care: more than watching patients swallow their pills
## Common Adverse Effects

| G.I. complaints | Ethionamide  
|                | Cycloserine  
|                | PAS  
|                | Fluoroquinolones  
|                | Clofazimine  
|                | Rifabutin  |
| Hepatotoxicity | INH  
| (early symptoms are anorexia and malaise, then abdominal pain, vomiting, jaundice) | Rifampicin/rifabutin  
|                | Ethionamide  
|                | PZA  
|                | PAS  
|                | Fluoroquinolones |
# Common Adverse Effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>INH, Ethionamide, Cycloserine, Linezolid, Linezolid, Ethambutol</td>
</tr>
<tr>
<td>Rash</td>
<td>All</td>
</tr>
<tr>
<td>Headache</td>
<td>Fluoroquinolones, Isoniazid, Cycloserine, Ethionamide, Ethambutol</td>
</tr>
<tr>
<td>Seizures</td>
<td>Cycloserine</td>
</tr>
<tr>
<td>Common Adverse Effects</td>
<td>Drugs</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Ethionamide, PAS</td>
</tr>
<tr>
<td>Hearing loss, Vestibular toxicity</td>
<td>Aminoglycosides, Capreomycycin</td>
</tr>
<tr>
<td>Behavioral changes</td>
<td>Cycloserine, Ethionamide, Isoniazid, Fluoroquinolones</td>
</tr>
<tr>
<td>Visual changes</td>
<td>Ethambutol, Rifabutin, Isoniazid, Linezolid</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Aminoglycosides, Capreomycycin</td>
</tr>
<tr>
<td>Hypokalemia, Hypomagnesemia</td>
<td></td>
</tr>
</tbody>
</table>
TO 28: Personal Impact

A Major Human Cost
Of those treated for drug-resistant TB:

- **9%** Die During Treatment
- **27%** Stop Working
- **73%** Hospitalized
- **37%** Require Home Isolation

Source: Suzanne Marks, CDC/Division of Tuberculosis Elimination
“Findings from TBESC Task Order 28” Presentation at NTCA, 6/12/2014
The public sector covered: 80% of MDR and 100% of XDR TB costs

Source: Suzanne Marks, CDC/Division of Tuberculosis Elimination “Findings from TBESC Task Order 28” Presentation at NTCA, 6/12/2014

The Outsized Financial Toll of MDR and XDR TB
Cost increases with greater resistance:

- Productivity loss during treatment
- Direct treatment costs, including:
  - Drugs & diagnostics
  - Case management & social work
  - Housing & transportation
  - Hospitalization

Average Treatment Costs, Per Case (2010 dollars)

- TB Treatment: 6-9 mo. $17,000
- MDR TB Treatment: 20-26 mo. $260,000
- XDR TB Treatment: 32 mo. $554,000

$0 $150,000 $300,000 $450,000 $600,000

$134,000 $126,000 $124,000

$430,000 $554,000
Comparison of Direct Costs:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cost in 2010 Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR TB episode</td>
<td>$134,000</td>
</tr>
<tr>
<td>XDR TB episode</td>
<td>$430,000</td>
</tr>
<tr>
<td>Pneumococcal Disease episode</td>
<td>$47,000</td>
</tr>
<tr>
<td>Breast Cancer, lifetime</td>
<td>$20,000-$100,000</td>
</tr>
<tr>
<td>HIV Infection, lifetime</td>
<td>$380,000</td>
</tr>
</tbody>
</table>

Source: Suzanne Marks, CDC/Division of Tuberculosis Elimination “Findings from TBESC Task Order 28” Presentation at NTCA, 6/12/2014
TO 28: MDR Outcomes

2005-2007 random sample MDR cases from CA, TX, NYC (N=135, of total US 370)

- 21% Acquired resistance (any)
- 90% Ambulatory care (>80% doses done as outpt)
- 73% were hospitalized 1-6 times during course
- 90% assigned case managers
- 81% documented expert consultation
- 97% culture conversion if eligible (median 2 mos)
- 78% Treatment completion
- 9% died during treatment, 2% lost to follow-up

Marks S., Emerging Infectious Diseases, May 2014
Management of Drug-Resistant TB

Summary:

- Treatment of MDR-TB is complex and costly
- *It is much easier to prevent than to treat*
- Expert consultation should be obtained whenever possible when MDR- or XDR-TB is suspected

Preventable, Treatable, Curable