Drug-resistant TB
CITC Virtual TB Intensive, October 2020

Lisa Chen MD
Professor of Medicine
CITC/University of California San Francisco

Chris Keh MD
Public Health Medical Officer
CA Department of Public Health
Overview

• DR-TB definitions & US epidemiology (re-cap)
• Predictors for drug-resistance
• Clinical application: molecular/phenotypic drug-sensitivity tests (DSTs)
• Building a DR-TB regimen
• Case management & side effect monitoring
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)
MDR Care = team sport
Drug-resistant TB in US

What’s the likelihood of caring for a case in your clinic?

(CHAT: How many MDR cases in past year have you seen?)
Cases of MDR TB by History of TB, United States 1993 – 2018*

In 2018:
- 98 total cases MDR (1.5%); (79 cases primary)
- 85% of primary MDR were foreign-born
- 1 case of XDR (range 0-10 per year)
Primary Anti-TB Drug Resistance: INH-mono-resistant vs MDR-TB
United States, 1993 – 2017

Note: Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.
Case scenario: DR-TB risk factors

when should we suspect drug-resistance?
Case 1

• 21-year-old Filipina woman with Type I DM recently immigrated 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 (HRZE) 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: Gisela Schecter, MD
Case 1
Case 1
Case 1
Case 1
Case 1
Case 1

- 21-year-old Filipina woman with Type I DM recently immigrated 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 (HRZE) given by SAT last year.

**Where are the high-risk areas in the world?**

(CHAT: Name ex. DR-TB high burden countries of significance to TB work in your practice)

- Presented with cough x 5 months, progressive SOB/DOE x 6 weeks, pleuritic chest pain and fever to 101 degrees.
MDR among notified TB cases
WHO report 2019

Estimated incidence of MDR/RR-TB in 2018, for countries with at least 1000 incident cases

Estimated global incidence and proportion of MDR among TB cases

• 484,000 incident cases of MDR
• 3.4% of all new cases and 18% of previously treated cases have MDR
• Of notified cases – half are from India (27%), China (14%), and the Russian Federation (9%)
Case 1

• 21-year-old Filipina woman with Type I DM recently immigrated 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 (HRZE) 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: Gisela Schecter, MD
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 $10^6$

$INH \times RIF = 10^6 \times 10^8 = 10^{14}$

Need a drug COMBINATION approach & programmatic support for cure
Predictors for Drug-resistance

• History of prior therapy (most powerful predictor) or failing current 1st-line rx (lack cx conversion within 3mo)

• Foreign-born/frequent travel from countries or ethnicities with high prevalence of MDR
  • Look at LOCAL data/risk groups: Ex. Hmong refugees

• Known contact to DR-TB case

• Presence of RIF-resistance predicts MDR

• HIV+ (higher incidence of RIF mono-resistance)
Diagnostics
Case: 31 yo M with HIV and cough x 1 yr

- Hemoptysis, 30 kg weight loss, fatigue
- Has been living in Thailand for years
- CD4=280, VL ND, on ART
- Presented to ER on 5/3
- Sputum smear = numerous AFB on 5/4
- What do you order?
- GeneXpert = POSITIVE MTB, RIF resistance DETECTED on 5/4
- Active TB regimen (expanded) started 5/4
Current Molecular Diagnostics

- NAAT/Beacon (e.g. Xpert MTB/RIF)
- Pyrosequencing
- Sanger Sequencing (Molecular Detection of Drug Resistance “MDDR”, CDC)
- Next Generation Sequencing (tNGS)
  - Whole Genome Sequencing
  - Targeted NGS

Chapter 3, page 48
Rapid Molecular Testing - Benefit

• Short turnaround time (compared to phenotypic methods)
  • Earlier initiation of effective tx
  • Decreased period of infectiousness
  • Improved pt outcome
  • Earlier involvement of MDR expert
  • Earlier request for 1st/2nd line susceptibilities

• High stakes setting
  • MDR suspect
  • Pregnancy
  • HIV/immunocompromised
  • Do Not Board decisions
  • Public health settings (shelter, congregate, schools)
Rapid Molecular Testing - points to consider

- False negatives may occur
  - Inhibitors
  - Low DNA load
  - NTM/mixed

- Results can help to guide early changes in treatment, but must always be confirmed with phenotypic data (susceptibility testing)
## Molecular Testing: Drugs/Loci

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Gene/locus</th>
<th>Sensitivity (Sequencing)</th>
<th>Specificity (Sequencing)</th>
<th>Assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td><em>katG</em></td>
<td>86.0</td>
<td>99.1</td>
<td>Hain, PSQ, MDDR</td>
</tr>
<tr>
<td>INH and Ethionamide</td>
<td><em>inhA</em> promoter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH</td>
<td><em>ahpC</em> promoter</td>
<td>4.5</td>
<td>100</td>
<td>PSQ</td>
</tr>
<tr>
<td>INH</td>
<td><em>fabG1</em></td>
<td></td>
<td></td>
<td>PSQ, MDDR</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td><em>rpoB</em></td>
<td>97.1</td>
<td>97.4</td>
<td>Xpert, Hain, PSQ, MDDR</td>
</tr>
<tr>
<td>Ethambutol (EMB)</td>
<td><em>embB</em></td>
<td>78.8</td>
<td>94.3</td>
<td>Hain, MDDR</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td><em>pncA</em></td>
<td>86.0</td>
<td>95.9</td>
<td>MDDR</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td><em>gyrA</em></td>
<td>79.0</td>
<td>99.6</td>
<td>Hain, PSQ, MDDR</td>
</tr>
<tr>
<td>Amikacin (AMK)</td>
<td><em>rrs</em></td>
<td>90.9</td>
<td>98.4</td>
<td>Hain, PSQ, MDDR</td>
</tr>
<tr>
<td>Capreomycin (CAP)</td>
<td><em>rrs</em></td>
<td>55.2</td>
<td>91.0</td>
<td>MDDR</td>
</tr>
</tbody>
</table>


Types of mutations

Silent (synonymous)
- Nucleic acid change
- No amino acid change
- Not associated with drug resistance generally
  - 514 (TTC→TTT) mutation in rpoB is the most common silent mutation

Missense (nonsynonymous)
- Nucleic acid change
- Amino acid change
- Some are associated with resistance
Current Molecular Diagnostics

- NAAT/Beacon (e.g. Xpert MTB/RIF)
- Pyrosequencing
- Sanger Sequencing (Molecular Detection of Drug Resistance “MDDR”, CDC)
- Next Generation Sequencing (tNGS)
  - Whole Genome Sequencing
  - Targeted NGS

Chapter 3, page 48
Xpert MTB/RIF Test Performance

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear pos. TB</td>
<td>95-98%</td>
<td>99%</td>
</tr>
<tr>
<td>Smear neg. TB</td>
<td>60-72%</td>
<td></td>
</tr>
<tr>
<td>Rifampin “R”</td>
<td>98-99%</td>
<td>99-100%</td>
</tr>
</tbody>
</table>


- Provides both MTB identification and detection of RIF resistance (rpoB)
- **RIF mono-resistance is rare; thus detection of RIF resistance on geneXpert is a red flag for possible MDR.**
- Run-time ~2 hours
- May give false negative if low DNA copies
- May yield no results if inhibitors present
Xpert MTB/RIF Report

• MTB DETECTED or NOT DETECTED
• Rif Resistance DETECTED or NOT DETECTED

• Not useful to follow once positive (DNA can be detected even after completion of adequate tx).
Xpert Probes: Coverage of $rpoB$

Most common silent mutation (433 TTT)

Location of silent mutation

Most common resistance mutation (450 TTG)

Location of missense mutation
Xpert Probe B mutation might be silent

- ~20% of all mutations detected in the *rpoB* core region are Silent!
  (In California and other low MDR areas)
- Most common is 433TTT
- Mutations detectable by probe B:
  - 70% is this silent mutation
  - Disputed mutation: 435TAC, 435TTC,
  - RIF-R mutations: 435GTC, 432AAA, GAA, etc.
<table>
<thead>
<tr>
<th>Probe</th>
<th>CT</th>
<th>End-pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe D</td>
<td>24.8</td>
<td>144.0</td>
</tr>
<tr>
<td>Probe C</td>
<td>23.6</td>
<td>177.0</td>
</tr>
<tr>
<td>Probe E</td>
<td>0</td>
<td>2.0</td>
</tr>
<tr>
<td>Probe B</td>
<td>24.3</td>
<td>118.0</td>
</tr>
<tr>
<td>SPC</td>
<td>25.4</td>
<td>301.0</td>
</tr>
<tr>
<td>Probe A</td>
<td>23.2</td>
<td>109.0</td>
</tr>
</tbody>
</table>

MTB: detected
RIF: RIF-R detected
Comment: Likely a true RIF-R.
Experts on Xpert: A Laboratorian and a Clinician Discuss Interpretation of Xpert MTB/RIF Results

This 90-minute webinar discussed the principles of Xpert MTB/RIF testing, highlighting it as an important tool for the rapid diagnosis of TB and how to best utilize the tool. A laboratorian and a clinician reviewed the rules set by the manufacturer, presented cases that addressed pitfalls in interpretation of test results, and offered expert opinion on how to proceed. The training was created for physicians who diagnose and treat patients with TB. The webinar may also be of interest to microbiologists. The webinar content is more advanced, and does not spend time on the basics.

Current Molecular Diagnostics

- NAAT/Beacon (e.g. Xpert MTB/RIF)
- Pyrosequencing
- Sanger Sequencing (Molecular Detection of Drug Resistance “MDDR”, CDC)
- Next Generation Sequencing (tNGS)
  - Whole Genome Sequencing
  - Targeted NGS

### Current molecular methods for detection of drug resistance in *M. tuberculosis*

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Cepheid Xpert MTB/RIF</th>
<th>HAIN MTBDRplus &amp; MTBDRsl</th>
<th>Pyrosequencing* (Laboratory-developed, non-commercial tests)</th>
<th>Sanger sequencing* (Laboratory-developed, non-commercial tests)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen types</td>
<td>Real-time PCR Molecular beacon probes</td>
<td>PCR Line probes</td>
<td>PCR Pyrosequencing</td>
<td>PCR Sanger sequencing</td>
</tr>
<tr>
<td>Clinical specimen</td>
<td>Concentrated specimen</td>
<td>Concentrated specimen⁴</td>
<td>Concentrated specimen⁴</td>
<td>Concentrated specimen⁴</td>
</tr>
<tr>
<td>Concentrated specimen⁴</td>
<td>Culture</td>
<td>Culture</td>
<td>Culture</td>
<td>Culture</td>
</tr>
<tr>
<td>Testing time</td>
<td>2.5 h</td>
<td>6-7 h</td>
<td>5-6 h</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Drugs tested</td>
<td>Rif</td>
<td>INH, Rif (MDR/TBpul) EMB, FO, AK, CM, KM (MTBDR rif)</td>
<td>INH, Rif, EMB, FO, AK, CM, KM</td>
<td>INH, Rif, EMB, FO, AK, CM, KM, PZA</td>
</tr>
<tr>
<td>Results</td>
<td>Mutation detected or not detected</td>
<td>Mutation detected or not detected</td>
<td>Sequences provided</td>
<td>Sequences provided</td>
</tr>
<tr>
<td>No sequences provided</td>
<td>Sequences of a few frequent mutations are provided</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methodology limitations</td>
<td>Difficult to detect mixed susceptible and resistant population</td>
<td>Difficult to detect mixed susceptible and resistant population</td>
<td>Mixed population can be detected, but the sensitivity has not been well characterized</td>
<td>Mixed population can be detected, but the sensitivity has not been well characterized</td>
</tr>
<tr>
<td>Silent mutations and mutations not conferring resistance lead to false resistance interpretation</td>
<td>Silent mutations and mutations not conferring resistance lead to false resistance interpretation</td>
<td>Not suitable for detecting mutations spread throughout a gene (e.g., pncA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chapter 3, page 48
Pyrosequencing (PSQ) REPORT

PSQ is a rapid screening technique for molecular detection of drug resistance. For confirmation of the PSQ results, culture-based drug susceptibility testing should be performed. A negative result (e.g. no mutation) does not rule out contributory mutations present elsewhere in the genome.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTBC</td>
<td>MTBC (not M. bovis)</td>
<td>DNA of MTB complex detected (not M. bovis).</td>
<td></td>
</tr>
<tr>
<td>INH</td>
<td>katG (313-316)</td>
<td>Ser(AGC)315Thr(ACC)</td>
<td>Associated with INH resistance.</td>
</tr>
<tr>
<td>INH</td>
<td>inhA promoter</td>
<td>No mutation</td>
<td></td>
</tr>
<tr>
<td>INH</td>
<td>ahpC promoter</td>
<td>No mutation</td>
<td></td>
</tr>
<tr>
<td>INH</td>
<td>fabG</td>
<td>No mutation</td>
<td></td>
</tr>
<tr>
<td>RIF</td>
<td>rpoB (RRDR)</td>
<td>His(CAC)526Tyr(TAC)</td>
<td>Associated with Rifampin &amp; Rifabutin resistance.</td>
</tr>
<tr>
<td>RIF</td>
<td>rpoB176</td>
<td>No mutation</td>
<td></td>
</tr>
<tr>
<td>AMK,CAP,KAN</td>
<td>rrs (1397-1406)</td>
<td>No mutation</td>
<td>Suggests susceptibility to amikacin, kanamycin and capreomycin.</td>
</tr>
<tr>
<td>Quinolones</td>
<td>gyrA (QRDR)</td>
<td>No mutation</td>
<td>Suggests susceptibility to quinolones</td>
</tr>
</tbody>
</table>
Current Molecular Diagnostics

- NAAT/Beacon (e.g. Xpert MTB/RIF)
- Pyrosequencing
- Sanger Sequencing (Molecular Detection of Drug Resistance “MDDR”, CDC)
- Next Generation Sequencing (tNGS)
  - Whole Genome Sequencing
  - Targeted NGS
Rapid Molecular Testing to Identify Drug Resistance

- Sequencing ("MDDR" at CDC)
  - Short turnaround time
  - Screen for resistance: INH, RIF, **EMB, PZA**, FQ, injectable
  - Reports specific mutation
  - Smear positive sputum or culture
  - Requested by/through state public health lab
MDDR submission criteria

• High-risk of RMP resistance or MDR TB
• Known RMP resistance (by rapid test or by culture-based DST)
• High public health impact (e.g., daycare workers, nurses)
• Adverse reactions to critical anti-TB drug (e.g. allergy to RMP)
• Mixed or non-viable cultures
• Isolates which fail to grow in DST medium

Results for Molecular Detection of Drug Resistance (Sanger Sequencing, complete panel); Conventional Drug Susceptibility Test in progress.

<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; CAC&gt;TAC; His525Tyr</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>No mutation</td>
<td>Isoniazid resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are INH-R.)</td>
</tr>
<tr>
<td>ketG (Ser315 codon)</td>
<td>Mutation; AGC&gt;ACC, Ser315Thr</td>
<td></td>
</tr>
<tr>
<td>embB (Met306,Gly406)</td>
<td>No mutation</td>
<td>Cannot rule out ethambutol resistance. (78% of EMB-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)</td>
</tr>
<tr>
<td>pncA (promoter, coding region)</td>
<td>No mutation</td>
<td>Cannot rule out PZA resistance. (86% of PZA-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 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>rrs (1400 region)</td>
<td>No mutation</td>
<td>Cannot rule out resistance to injectable drugs (kanamycin, capreomycin, amikacin). (In our in-house evaluation of 550 clinical isolates:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 91% of AMK-R isolates have a mutation in the rrs locus;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 87% of KAN-R isolates have a mutation in either the rrs locus or the els locus;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 65% of CAP-R isolates have a mutation in either the rrs locus or the tlyA locus.)</td>
</tr>
<tr>
<td>els (promoter)</td>
<td>No mutation</td>
<td></td>
</tr>
<tr>
<td>tlyA (entire ORF)</td>
<td>No mutation</td>
<td></td>
</tr>
</tbody>
</table>

*A negative result (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 Laboratory. They have not been cleared or approved by the Food and Drug Administration.
Remember! Drug Susceptibility Testing (DST)

• Smear and culture (drug susceptibility testing) remain the gold standard
• 1\textsuperscript{st}-line DST at local / commercial labs
• Many states perform basic 2\textsuperscript{nd}-line DST
• CDC performs expanded 2\textsuperscript{nd}-line DST
CDC- Drug Susceptibility Testing (DST)

- Isoniazid
- Rifampin
- Ethambutol
- Ciprofloxacin
- Ofloxacin
- Streptomycin
- Kanamycin
- Capreomycin

- Amikacin
- Rifabutin
- Ethionamide
- Para-aminosalicylic acid (PAS)
- Pyrazinamide*
- Bedaquiline**
- Linezolid**
- Clofazimine**

* Tested by MGIT 960 (all others indirect agar proportion)
** Available upon request

*** Cycloserine is not part of DST panel; may need to order this from another reference laboratory.
Limitations / Areas for Caution

• Molecular tests vs. DST discordance
  • Undescribed mutations outside of loci in current molecular tests → resistance
  • Emerging resistance in mixed populations may not be detected
  • “Disputed” mutations- DSTs show susceptible but associated with clinical treatment failure
How to interpret results of molecular tests for resistance
Case 1

- 70 yo asymptomatic man from India with abnormal preimmigration CXR, no TB history
- Domestic CXR with multifocal infiltrates
- Sputum smear positive x 3
- Xpert positive: rifampin resistant

What do you do next?
- Start MDR treatment
- Order pyrosequencing or MDDR
- Start RIPE
- Repeat Xpert on another specimen
- Start treatment for monoRif resistance
Case 1

• Treatment held; PSQ available within 2 days and clinically stable

• Pyrosequencing:
  • \textit{katG} mutation: INH R
  • \textit{rpoB} 531TTG mutation: RIF R
  • \textit{gyrA} (FQ): no mutations
  • \textit{rrs} (amikacin): no mutations

What do you do next?

• Start MDR treatment
• Order MDDR
• Start RIPE
• Repeat Xpert on another specimen
• Order second line DSTs
• Cancel DSTs
  (already have molecular results)
Case 2

• 70 yo man from Mexico in US x 25 years with 4 weeks of cough, no TB history
• CXR with multifocal infiltrates
• Sputum smear positive x 3
• Xpert positive, rifampin resistant

What do you do next?
• Start MDR treatment
• Order pyrosequencing or MDDR
• Start RIPE
• Repeat Xpert on another specimen
• Start treatment for monoRif resistance
Case 2

• RIPE started
• PSQ:
  • *katG/inhA*: no mutation
  INH Sens
  • *rpoB*: 514TTT silent mutation: RIF Sens
10-minute stretch break!

(Up next: Building a DR-TB regimen; Case management & side effect monitoring)
hope on the horizon
DR-TB TREATMENT: Updated Guidelines!

  Using individual patient data meta-analysis (IPDMA) from 12,030 patients (50 studies) across 25 countries


- CICT DR-TB Survival Guide 2016 (update in progress....)

http://www.currytbcenter.ucsf.edu

First step:
Consult with experts

FOR WESTERN US REGION:
CITC TB Warmline Consultation
Curry International Tuberculosis Center
1-877-390-NOTB  or  1-877-390-6682
www.currytbcenter.ucsf.edu

FOR CA STATE:
CA DPH: MDR-TB Service
Provides clinical consultation, case management, CI assistance
510-620-3000
How many drugs for MDR?

Goal: At least 5 drugs in intensive phase (IP) & 4 drugs in continuation phase (CP)

- Studies suggest better outcomes with at least 5 drugs (IP)
  - *Drugs of poor or doubtful efficacy should not be added purely to ensure #*

- Expert input:
  - Consider more if extensive disease and/or resistance
  - Four may be sufficient with limited disease and/or limited resistance
  - Also consider relative contributions of each drug (strength/weakness)

- [WHO 2016 & 2020 – at least 4 IP then 3 CP “likely effective” drugs]
## Reclassified DR-TB Medications

<table>
<thead>
<tr>
<th>Choice</th>
<th>ATS/CDC/ERS/IDSA</th>
<th>WHO Group A: Include all three</th>
<th>Levofloxacin OR Moxifloxacin</th>
<th>WHO Group B: Add one or both</th>
<th>WHO Group C: Add to complete the regimen [WHO ranking by relative balance of benefit to harm: E, Dlm, Z, Ipm-Cln, Mpm, Am (S), Eto (Pto), PAS; no HD Inh included]</th>
<th>First line drugs demoted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Choose one FQ</td>
<td></td>
<td>Bedaquiline</td>
<td>Clofazimine</td>
<td>Amikacin (OR Streptomycin)</td>
<td>Order FQ rapid molecular &amp; SL-DST if RIF-R</td>
</tr>
<tr>
<td>2.</td>
<td>Use BDQ and LZD</td>
<td></td>
<td>Linezolid</td>
<td>Cycloserine</td>
<td>Delamanid</td>
<td>BDQ and LZD for all cases (BDQ for age 6y+)</td>
</tr>
<tr>
<td>3.</td>
<td>Use CFZ and CS</td>
<td></td>
<td></td>
<td></td>
<td>Ethambutol</td>
<td>Need to address access!</td>
</tr>
<tr>
<td>4.</td>
<td>Add inj. as needed</td>
<td></td>
<td></td>
<td></td>
<td>Pyrazinamide</td>
<td>No injectable for most!! (No capreomycin for any)</td>
</tr>
<tr>
<td>5.</td>
<td>Add as needed</td>
<td></td>
<td></td>
<td></td>
<td>Ethionamide</td>
<td>First line drugs demoted</td>
</tr>
<tr>
<td>6.</td>
<td>Add as needed</td>
<td></td>
<td></td>
<td></td>
<td>Imipenem-cilastatin OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Meropenem (PLUS clavulanate)</td>
<td></td>
</tr>
</tbody>
</table>

Comparison 2019 ATS/CDC/ERS/IDSA guidelines and 2016 & 2020 WHO
Data for recommendations from meta-analysis (not RCTs)

• Individual patient data meta-analysis, n=13,104
• Propensity score matched (attempt to control for differences)
• Drugs analyzed only when susceptible
Use these drugs

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Treatment failure or relapse versus treatment success</th>
<th>Death versus treatment success</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin OR moxifloxacin</td>
<td>3 143 0.3 (0.1–0.5) 3 551 0.2 (0.1–0.3)</td>
<td></td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>1 391 0.3 (0.2–0.4) 1 480 0.2 (0.2–0.3)</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>1 216 0.3 (0.2–0.5) 1 286 0.3 (0.2–0.3)</td>
<td></td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clofazimine</td>
<td>991 0.3 (0.2–0.5) 1 096 0.4 (0.3–0.6)</td>
<td></td>
</tr>
<tr>
<td>Cycloserine OR terizidone</td>
<td>5 483 0.6 (0.4–0.9) 6 160 0.6 (0.5–0.8)</td>
<td></td>
</tr>
</tbody>
</table>

< 1.0 is good

Don’t use these drugs

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Treatment failure or relapse versus treatment success</th>
<th>Death versus treatment success</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number treated</td>
<td>Adjusted odds ratio (95% confidence limits)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>2,946</td>
<td>1.9 (1.0–3.4)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>777</td>
<td>2.0 (1.1–3.5)</td>
</tr>
<tr>
<td>Amoxicillin–clavulanic acid</td>
<td>492</td>
<td>1.7 (1.0–3.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Treatment failure or relapse versus treatment success</th>
<th>Death versus treatment success</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number treated</td>
<td>Adjusted odds ratio (95% confidence limits)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>1,163</td>
<td>0.4 (0.1–1.0)</td>
</tr>
<tr>
<td>Delamanid</td>
<td>289</td>
<td>1.1 (0.4–2.8)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1,248</td>
<td>2.7 (0.7–10.9)</td>
</tr>
<tr>
<td>Imipenem–cilastatin OR meropenem</td>
<td>206</td>
<td>0.4 (0.2–0.7)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>635</td>
<td>0.3 (0.1–0.8)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>226</td>
<td>0.5 (0.1–2.1)</td>
</tr>
<tr>
<td>Ethionamide OR prothionamide</td>
<td>2,582</td>
<td>1.6 (0.5–5.5)</td>
</tr>
<tr>
<td>p-aminosalicylic acid</td>
<td>1,564</td>
<td>3.1 (1.1–8.9)</td>
</tr>
</tbody>
</table>
**MDR-TB Treatment Principles**

- Seek expert consultation
- Never add a single drug to a failing regimen

**When choosing drugs:**

- Consider cross-resistance (refer to Chap 4/Table 2)
  - low level INH-R (*inhA, ahpC, fabG*) → 70% Ethionamide R
  - Moxifloxacin → Levofloxacin
  - Clofazimine ↔ Bedaquiline
- Consider side-effects
- Avoid drugs used previously to treat patient’s TB
**Medication Fact Sheets**

- Drug class/trade name
- Activity against TB
- Cross-resistance
- Dose (adult, peds, renal)
- Route of administration
- Preparation/storage
- Pharmacokinetics
- Oral absorption/metabolism
- CSF penetration
- Special circumstances
- Adverse reactions/contraindications
- Monitoring
- Costs/patient education
Linezolid (Zyvox)

- Excellent activity against *M. tb in vitro*
- Dose - 600 mg po qd (case series using 300mg daily)
  - Evidence suggests fewer SE if maintain trough <2 ug/ml
  - Experts: consider 600mg qod dosing or 300mg qd if AE (ideally post-culture conversion)
- 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
Bedaquiline (Situro)

• 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

CHAT: How many cases have you started on BDQ?
CDC Provisional Guidelines for Use of Bedaquiline 2013

CDC MMWR 2013;62;1-12

• “When an effective treatment regimen cannot be provided” but now key component of 2019 ATS/CDC/ERS/IDSA recommendations:
  • Used for 24 weeks of treatment in adults with confirmed MDR-TB
  • 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 Provisional Guidelines: Monitoring on Bedaquiline

- No dose adjustment with mild/mod renal impairment
- **Drug interactions** – metabolized through CYP3A (avoid w/RIF)
- **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

CDC MMWR 2013;62;1-12
We are using Bedaquiline more
BDQ use by year, CA MDR Service

Slide credit: Pennan Barry MD & Phil Lowenthal
We are using injectables less
Injectable use by year, CA MDR Service

% Patients on Injectable

0% 20% 40% 60% 80% 100% 120%

2015 2016 2017 2018 2019

Slide credit: Pennan Barry MD & Phil Lowenthal
Moving towards DR-TB all-oral regimens

**Status-quo**
- Very good TB outcomes with prior regimens (CA MDR 88% success)
- Can routinely provide appropriate monitoring (audiogram, electrolytes, creatinine, vestibular)

**All-oral**
- We do see (and worry about) hearing loss/tinnitus
- PICC / IM injections carry risk or pain
- Injectable administration is inconvenient and expensive
- We have other/new options!

**CHAT:** Have you moved towards all-oral MDR regimens?
MDR-TB Treatment Duration

2019 ATS/CDC/ERS/IDSA guidelines:
Utilize culture conversion to help guide minimum duration.
Consider clinical context, extent of disease, & response to treatment when determining final durations within ranges given:

- **Intensive phase:** at least 5-7 mo after culture conversion for use of injectable agent; [how IPDMA applies to non-injectibles?; studies of BDQ x6mo ongoing]
- **Total duration:** at least 15-21 months after culture conversion
- **Pre-XDR & XDR:** total duration at least 15-24mo after culture conversion

[CITC Survival Guide: IP at least 6mo after culture conversion; total at least 18m after culture conversion – update pending]
“Taking medications is not easy. They taste bad and they make my stomach upset. After I take them, I don’t like anyone to talk to me. It takes a while before I feel better. I know it is my obligation and responsibility, but how much longer must I take them?”

Participant/PhotoVoice

Less time on medicines
Makes a difference to the lives involved
Standardized Shorter Treatment Regimen for MDR (STR) “Bangladesh Regimen”; (9-12 mo)

- Recommended by WHO 2016 as “standardized” option
- Observational data - impressive treatment success 84.5% (n=515); (Aung et al. Int J Tuberc Lung Dis 2014)
- STREAM Trial (Nunn et al. NEJM 2019): RCT noninferior c/w WHO standardized regimen; similar safety, no diff AE n=424 MDR; 33% HIV+)
- Contraindications: resistance to any drug in regimen, extrapulmonary disease, pregnancy
- WHO 2019 IPDMA: STR did less well if resistance to drugs in regimen and when Long regimen contained newer/better drugs

## Short(er) Treatment Regimen (STR) for MDR-TB

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Phase (7 drugs)</th>
<th>Continuation Phase (4 drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin*</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Isoniazid*</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

*High dose

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Barriers to Implementing STR

Can STR be used in the U.S.?

• Few qualify by strict criteria (15% in California)
• Unclear efficacy effect if substitute for adverse events or resistance
• Clofazimine availability problematic for some
• Contains injectable
BPaL: NIX-TB Trial
(Conradie et al, NEJM Mar 2020)

- Phase 3, multicenter (3 sites/South Africa), open-label, single-arm study
- N=109: XDR-TB (65%) or MDR-TB (intolerant/non-responsive: 35%)
- Efficacy results: 90% of patients with highly-resistant TB achieved relapse-free cure status 6 months after end of treatment
  - Median time to culture < 6 weeks
- Limitations: Small, single study/country, no randomized control group
  - Await final 24mo relapse data (early 2021?)
  - [FDA brochure lists 3 relapse pt. at 15mo]
Nix-TB (BPaL) regimen

- Pretomanid 200 mg qd
- Bedaquiline 200 mg tiw after 2 week load (400mg qd)
- Linezolid 1200mg qd*

*Amended from 600mg bid

Extend 3 additional months if culture+ at wk 16

Photo credit: Francesca Conradie
Pretomanid: New Chemical Entity Developed Specifically to Treat TB

- Nitroimidazooxazine with novel mechanisms of action
- Possesses bactericidal and sterilizing activities
- Nonclinical and clinical studies showed anti-TB activity against drug-susceptible and drug-resistant M.tuberculosis
- Studied in 1168 individuals, 19 clinical studies

Kills replicating and non-replicating Mtb

PRETOMANID

Actively replicating MTB under aerobic conditions
- Inhibits cell wall production through blockage of mycolic acid biosynthesis

Non-replicating MTB under hypoxic conditions
- Acts to kill mycobacteria following nitric oxide release

Slide credit: Francesca Conradie
Dose Modifications

- **BPaL regimen**: 6-mo all oral regimen (administered with food; 7d/wk)
  - Regimen could be interrupted for up to 35 consecutive days
  - Missed doses of regimen made up at end of treatment

- **Linezolid**: Could be reduced, temporarily interrupted or discontinued after 1mo
  - All pts. got 1200mg (or 600 bid) first month (& did fairly well)
  - 16 (15%) completed 6mo at 1200mg
  - 50 (46%) interrupted LZD and resumed same or lower dose
  - 33 (30%) permanently d/c LZD; with all surviving pt. (27) completing rx
NIX-TB: Adverse events

• 100% had at least 1 AE
• 19 (17%) serious AE; 62 (57%) grade 3-4; unrelated to HIV
• 88 (81%) peripheral neuropathy (most mild-mod);
  • No difference in HIV status or LZD 600 bid vs 1200 qd dosing
  • Majority after 3mo
• 2 optic neuritis (resolved after d/c LZD)
• 52 (48%) myelosuppression; managed w/ interruption & decr.
  • 40 (37%) anemia – majority within first 2 mo
• 17 with ALT/AST >3x ULN (2 with incr. Tbili)
  • 8 had rx held; all had rx restarted and completed 6mo
• No QT >480 msec
FDA Approval: BPaL Regimen  
August 2019

BPaL = Bedaquiline (B), Pretomanid (Pa), Linezolid (L)

FDA Approves New Treatment for Highly Drug-Resistant Forms of Tuberculosis

Pretomanid approved “as part of a three-drug, six-month, all oral regimen for the treatment of people with XDR-TB or MDR-TB who are treatment-intolerant or non-responsive (collectively ‘highly drug-resistant TB’).”

…..varied uptake/practice thus far in US, approx. 30+ cases on BPaL, collecting data….do with expert consultation

TB Alliance: tballiance.org
Surgery + MDR regimen

ATS/CDC/ERS/IDSA Guidelines 2020

• Meta-analysis, systematic reviews, & IPDMA

• Limited evidence: Net benefit of elective partial lung resection (lobectomy/wedge) together with MDR rx

• Consider if:
  — Strong risk for relapse or failure on medical rx alone

• No evidence to support pneumonectomy + medical rx
Treatment Regimens for MDR-TB Contacts
ATS/CDC/ERS/IDSA 2019 Guidelines

- 6-12 mos later-generation FQ monotherapy
- Or FQ combined with second agent (ex. FQ/EMB)
  - PZA should not routinely be used as second agent (toxicity/adverse effects)
  - If FQ-resistant (pre-XDR/XDR) may consider PZA/EMB
- LTBI regimen should be based on drug-sensitivity of source
- Expert opinion: if unable to use acceptable options, consider monitor for 2 years in lieu of rx
Case Management
Side Effects
Monitoring
MDR TB Case Management

• Seek consultation with MDR TB expert as soon as multidrug resistance is known or suspected

• Use daily DOT throughout entire treatment course
  • No intermittent therapy for drug resistance!!

• Use case management tools (drug-o-gram) to follow serial changes in drugs, bacteriology, CXR, toxicities

• Optimize management of underlying medical conditions and nutritional status (i.e. diabetes)
### TREATMENT REGIMEN

<table>
<thead>
<tr>
<th>Date</th>
<th>Wt.</th>
<th>INH</th>
<th>RIF</th>
<th>PZA</th>
<th>EMB</th>
<th>SM</th>
<th>KM</th>
<th>V B6</th>
<th>CM</th>
<th>PAS</th>
<th>CFZ</th>
<th>MFX</th>
<th>LNZ</th>
<th>CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/21/11</td>
<td>1000</td>
<td>900</td>
<td></td>
<td>800</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>600</td>
</tr>
<tr>
<td>1/24/11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/28/11</td>
<td>hold</td>
<td>hold</td>
<td>hold</td>
<td>hold</td>
<td>hold</td>
<td>hold</td>
<td>hold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/9/11</td>
<td>500</td>
<td>4gm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/11/11</td>
<td>64 kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/17/11</td>
<td></td>
<td></td>
<td>100</td>
<td>800</td>
<td>500</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/18/11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/25/11</td>
<td>52 kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/07/11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/08/11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### BACTERIOLOGY

<table>
<thead>
<tr>
<th>Date</th>
<th>spec</th>
<th>smi/cult</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/28/11</td>
<td>sp</td>
<td>neg/pre</td>
<td>1/27/11: CDC MDDR results; multiple mutations</td>
</tr>
<tr>
<td>2/8/10</td>
<td></td>
<td></td>
<td>2/8/10: Case Conference—Expanded regimen recommended.</td>
</tr>
<tr>
<td>2/9/11</td>
<td>sp</td>
<td>neg/pre</td>
<td>2/9/11: CXR: Enlarging mass RUL</td>
</tr>
<tr>
<td>2/25/11</td>
<td>sp</td>
<td>Neg/pre</td>
<td>3/7/11: CT stable RUL node 2x2 cm. fibrotic scarring LUL</td>
</tr>
<tr>
<td>3/02/11</td>
<td>sp</td>
<td>1++</td>
<td></td>
</tr>
</tbody>
</table>

### SUSCEPTIBILITY RESULTS

<table>
<thead>
<tr>
<th>Date</th>
<th>Spec.</th>
<th>Lab</th>
<th>INH</th>
<th>RIF</th>
<th>EMB</th>
<th>PZA</th>
<th>SM</th>
<th>KM</th>
<th>V B6</th>
<th>CM</th>
<th>PAS</th>
<th>ETA</th>
<th>LFX</th>
<th>MFX</th>
<th>LNZ</th>
<th>CS</th>
<th>RFB</th>
<th>CFZ</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/02/10</td>
<td>Biopsy</td>
<td>MDL</td>
<td>R:0.1</td>
<td>R:1.0</td>
<td>R:5.0</td>
<td>R:100</td>
<td>R:1.0</td>
<td>R:1.5</td>
<td>R:3.0</td>
<td>R:3.0</td>
<td>R:5.0</td>
<td>R:0.25</td>
<td>R:0.95</td>
<td>LNZ</td>
<td>CS</td>
<td>RFB</td>
<td>CFZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/27/11</td>
<td>Sputum</td>
<td>OOPHIL</td>
<td>R:0.1</td>
<td>R:1.0</td>
<td>R:5.0</td>
<td>R:100</td>
<td>R:2.5</td>
<td>S:5.0</td>
<td>R:2.5</td>
<td>R:2.0</td>
<td>R:1.0</td>
<td>S:0.5</td>
<td>R:1.0</td>
<td>S:6.0</td>
<td>S:60</td>
<td>S:60</td>
<td>S:60</td>
<td>12/20/10</td>
<td></td>
</tr>
<tr>
<td>12/02/10</td>
<td>Biopsy</td>
<td>NJRL</td>
<td>R:2.5</td>
<td>R:8.0</td>
<td>R:8.0</td>
<td>S:8.0</td>
<td>S:8.0</td>
<td>S:8.0</td>
<td>S:60</td>
<td>S:60</td>
<td>3/10/11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Common Side Effects

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.I. symptoms</td>
<td>Ethionamide, PAS, Quinolones, Clofazimine, Rifabutin, Linezolid</td>
</tr>
<tr>
<td>Hearing loss, vestibular toxicity</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Renal insufficiency/Electrolyte</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>PZA, PAS, Rifabutin, Ethionamide, Quinolones</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Linezolid, INH, Quinolones, Ethionamide, Cycloserine</td>
</tr>
<tr>
<td>Neuropsychiatric: depression, agitation, psychosis, difficulty concentrating, insomnia</td>
<td>Cycloserine, Quinolones, Ethionamide</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>Bedaquiline, Clofazimine, Quinolones</td>
</tr>
<tr>
<td>Rash</td>
<td>All</td>
</tr>
<tr>
<td>Visual changes</td>
<td>EMB, Rifabutin, Linezolid</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Ethionamide, PAS</td>
</tr>
<tr>
<td>Headache</td>
<td>Quinolones, Cycloserine, Ethionamide, EMB</td>
</tr>
</tbody>
</table>
## Monitoring (drug dependent)

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKG/QTcF</td>
<td>Bedaquiline, fluoroquinolones or combined with other QTc prolonging agents</td>
</tr>
<tr>
<td>Audiology (monthly until 1 month post d/c)</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Linezolid, FQ</td>
</tr>
<tr>
<td>Depression screening (e.g. PSQ-9)</td>
<td>Cycloserine</td>
</tr>
<tr>
<td>Other (TSH, pregnancy, vestibular exam, labs, visual acuity/Ishihara)</td>
<td>By drug side effect</td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td>E.g. anti-depressants, QTc prolonging agents</td>
</tr>
</tbody>
</table>
QTc Prolongation

• Use Fredericia formula (most ECG machines use Bazett)

• QTc has substantial diurnal variation (up to 75ms)
  • Longest in AM

• Prolonged QTcF: >470 for females; >450 for men
  • Repeat ECG after 30 minutes to confirm
  • QTcF >500ms is more concerning; requires action

• Think about/address other prolonging drugs and conditions

Challenge TB 2018 QTc Guide:
Therapeutic Drug Monitoring (TDM)

- Some experts use routinely for all, while other choose specific drugs
- Consider more strongly in setting of kidney dysfunction or concerns for absorption
- Refer to Survival Guide for timing of trough/peak levels

- Cycloserine- highly recommended
  - Absorption variable
  - Therapeutic and toxic levels are very close
- Linezolid
  - Increased risk for toxicity with trough >2
  - Aminoglycoside
  - PAS, fluoroquinoline, ethionamide
# MDR Monitoring Checklist

<table>
<thead>
<tr>
<th>Date</th>
<th>CLINICAL MONITORING</th>
<th>LAB MONITORING FOR TOXICITY / COMORbidITIES</th>
<th>MONITORING PROCEDURES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sputum smear and culture</td>
<td>CBC</td>
<td>Audiogram</td>
</tr>
<tr>
<td></td>
<td>CXR</td>
<td>Creatinine</td>
<td>Vestibular exam</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
<td>LFTs</td>
<td>Vision Exam</td>
</tr>
<tr>
<td></td>
<td>Symptom review</td>
<td>K+, Ca, Mg++</td>
<td>Peripheral Neuropathy</td>
</tr>
<tr>
<td></td>
<td>DST</td>
<td>Drug Level</td>
<td>Arthralgias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TSH</td>
<td>Depression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Month of Treatment</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Important: Monitoring recommendations may change if treatment regimen or pt. status changes. A box indicates monitoring activity is recommended. Check box when activity is completed.

1 Collect three AFB smear and culture specimens every 2 weeks until smear conversion, and then 2-3 specimens monthly until cultures have converted to negative. Once cultures have converted, obtain at least 1 specimen monthly throughout therapy.
2 Obtain baseline CXR and monitor q 3 months during the first year and q 6 months in the second year of treatment.
3 Monitor weight monthly and adjust medications as needed.
4 Monitor for symptoms monthly.
5 Obtain first and second line DST results at baseline. Repeat if pt on RIF and remains culture positive prior to MDR Rx, and again if patient fails to convert culture after 3 months on treatment.
6 Obtain Creatinine at baseline and monthly while pt is on an injectable agent.
7 LFTs at baseline and then monthly while pt is on PZA, ethionamide or PAS.
8 K+, Ca++, and Mg++ at baseline and monthly while pt is on an injectable agent.
9 Drug level for injectable agent and cyclosorine should be obtained after 2 weeks on therapy and if signs of toxicity develop.
<table>
<thead>
<tr>
<th>Activity</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MONITORING PROCEDURES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audiogram 14</td>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Vestibular exam 15</td>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Vision Exam 16</td>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Peripheral Neuropathy 17</td>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Arthralgias 18</td>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Depression 18</td>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

*Important: Monitoring recommendations may change if treatment regimen or pt. status changes.

---

1. Collect three AFB smear and culture specimens every 2 weeks until smear conversion, and then 2-3 specimens monthly until cultures have converted to negative. Once cultures have converted, obtain at least 1 specimen monthly throughout therapy.
2. Obtain baseline CXR and monitor q 3 months during the first year and q 6 months in the second year of treatment.
3. Monitor weight monthly and adjust medications as needed.
5. Obtain first and second line DST results at baseline. Repeat if pt on RIPE and remains culture positive prior to MDR Rx, and again if patient fails to convert culture after 3 months on treatment.
6. Obtain weekly for first month, then monthly for pt.s on linezolid.
7. Obtain Creatinine at baseline and monthly while pt is on an injectable agent.
Case- An example of medication saga

- Hemoptysis, 30 kg weight loss, fatigue
- Has been living in Thailand for years
- CD4=280, VL ND, on ART
- Sputum smear = numerous AFB on 5/4
- GeneXpert = POSITIVE MTB, RIF resistance DETECTED on 5/4
- Initial start (2017): RIPE + FQ + amikacin + linezolid
- After PSQ, MDDR, DST adjusted to (R- R/I): PZA, FQ, amikacin, linezolid, bedaquiline (+/- PAS)

- PAS - GI upset, refused to take
- BDQ - QTc rise to 520, repeat fluctuated back down
- PZA - GI upset
- Linezolid - held multiple times as pt c/o blurry vision (ophtho urgent eval - needs glasses)
- Severe anxiety / depression, limited for therapy due to linezolid DDI
- Eventually ended on - FQ / linezolid / EMB
Monitor MDR-TB patients for treatment response

• Collect sputum monthly throughout
• End-of-treatment sputum for smear and culture
• CXR quarterly and at end of treatment
• Monitor for 2 years after treatment
  • Quarterly: first year, Q6 months: second year
Discussion: 68 yo F with MDR TB with nausea. On the following regimen:

* BDQ
* Levofloxacin
* Linezolid
* PAS
* Cycloserine
Just one example of the tools needed

- GI complaints (very common)-
  - Drug ramping (CS, PAS, ETA)
  - Supportive care (H2 blockers, PPI, antacids)
  - Split dosing (for some meds), QHS dosing, admin with food
  - Anti-emetics, pre-medication, benzodiazepines
  - Crushing, cutting, liquids, capsules surrounding tablets
  - Alternative: ginger, sea-band, lemon heads, other
  - Switching to IV formulation
  - PEG, J-tube
Case: 43 yo M recently immigrated from Philippines

- Severe back pain, fatigue, loss of appetite, weight loss
- Dx with **Pott’s Diseases C7-S1** based on FNA that was smear neg, culture pos
- Started on RIPE, but then PZA stopped due to uric acid elevation
- After 2 months of treatment, worsening back pain
- Repeat MRI with concern for progression of disease

- What are your questions?
88% of MDR cases have good outcomes
California 2009–2018

*Includes 1 patient with relapse 8 years later with matching genotype but nonMDR DSTs
Management of Drug-Resistant TB

Summary:

• Treatment of DR-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