Diabetes related TB
and a primer on
Therapeutic Drug Monitoring

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Infectious Diseases, International Health
Overview of diabetes (DM) and tuberculosis (TB) interaction

Local case study

Pathophysiology

Global case study: Dhaka, Bangladesh

The case for metformin

What we are doing in Virginia:
- screening for DM in TB patients (hemoglobin A1c)
- linkage to DM care (metformin)
- early therapeutic drug monitoring
- patient/provider education (DM-TB flipchart)
- future study of therapeutic drug monitoring from urine
Diabetes is consistently a risk factor for developing active TB

Severity of diabetes increases the risk for TB

42,000 adults >65 years old from Hong Kong*

Diabetes with HbA1C≥7 compared to <7; odds for developing active PTB were 3.63 (1.79-7.33)*

All cause mortality increased in diabetics during TB treatment (compared to non-diabetics)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Population with DM Deaths/Total</th>
<th>Population without DM Deaths/Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fielder, 2002</td>
<td>USA</td>
<td>13/22 (59%)</td>
<td>29/152 (19%)</td>
<td>3.80 (1.42, 10.16)</td>
</tr>
<tr>
<td>Oursler, 2002</td>
<td>USA</td>
<td>8/18 (44%)</td>
<td>14/108 (13%)</td>
<td>6.70 (1.57, 28.52)</td>
</tr>
<tr>
<td>Dooley, 2009</td>
<td>USA</td>
<td>6/42 (14%)</td>
<td>20/255 (8%)</td>
<td>6.50 (1.11, 38.20)</td>
</tr>
<tr>
<td>Wang, 2009</td>
<td>Taiwan</td>
<td>13/74 (18%)</td>
<td>11/143 (8%)</td>
<td>5.20 (1.77, 15.25)</td>
</tr>
</tbody>
</table>

Summary: 4.95 (2.69, 9.10)

Heterogeneity I-squared = 0% (0, 85)

Weights are from random effects analysis
A local case

70 year-old man was admitted to UVA this month with 2 weeks of fever.

ROS also elicits a chronic cough (which was not the patient’s primary complaint) and he notices a foreign body sensation in his throat for months.

Fever wakes him at night, though does not soak the bed sheets, and accompanied by significant malaise. He notes 6-7 kg weight loss over the past 3 months.

Now it gets even more interesting...

Patient is originally from Ghana and returned last week following a 6 month visit. In Ghana he was treated with an anti-malarial that did not help his cough or his fever. He denies known TB contacts.

He is HIV negative, but has a known history of HTN, BPH and Type II Diabetes (on oral medications— not regular fingerstick monitoring while in Ghana).

While sick, he boards an international flight for Charlottesville.
Multiple sputum specimens 2-3+ AFB smear pos

*M. tuberculosis* complex (Xpert)

Remainder of susceptibilities pending

Defervesced on INH, RIF, EMB, PZA
1994: MDR-TB patient flew 747 from Honolulu → Chicago → Baltimore

925 contacts, 802 responded to survey: 11 skin test conversions → more likely on the longer flight and proximity to index patient

Kenyon et al. NEJM 1996
TB more frequent in those with poor diabetes control

No “special insidiousness” of signs and symptoms in the “tuberculous diabetic”

Not explained by familial contact, occupation, race, poverty or alcoholism
## Attributable risk of TB from Diabetes > HIV in Texas/Mexico border

### Participants excluded due to missing data:
- TB ruled out \( (n=41)\)
- MOTT \( (n=14)\)
- Missing data required for TB or inconclusive TB\(^a\) diagnosis \( (n=41)\)
- Missing information required for diabetes classification\(^b\) \( (n=4)\)

### Total TB cases for analysis \( (n=233)\)
- South Texas \( (n=61)\)
- North-eastern Mexico \( (n=172)\)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Diabetes</th>
<th>HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>AR(_{exposed}) (%)(^a)</td>
</tr>
<tr>
<td>South Texas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20+ ( (n=61))</td>
<td>2.7 (1.6–4.4)</td>
<td>63</td>
</tr>
<tr>
<td>20–34 ( (n=20))</td>
<td>0.9 (0.1–6.8)</td>
<td>-9</td>
</tr>
<tr>
<td>35–64 ( (n=32))</td>
<td>5.1 (2.6–10.2)</td>
<td>80</td>
</tr>
<tr>
<td>65+ ( (n=9))</td>
<td>1.7 (0.5–5.8)</td>
<td>41</td>
</tr>
<tr>
<td>NE Mexico</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20+ ( (n=172))</td>
<td>3.1 (2.3–4.2)</td>
<td>68</td>
</tr>
</tbody>
</table>

\(^{a}\)TTD\(^{a}\) diagnosis; \(^{b}\)diabetes classification; \(^{c}\)below 0.05

Restrepo et al. *Bull WHO* 2011
Diabetes alters phagocyte chemotaxis, activation and antigen presentation in presence of *M. tuberculosis*

Monocytes from diabetic patients have impaired chemotaxis that does not improve with insulin\(^1\)

Mice with streptozotocin induced diabetes, macrophages had 1/10 of phagocytic activation, despite similar in vitro killing→ 90% died after *M. tuberculosis* challenge, compared to only 10% of non-diabetic mice\(^2\)

In TB patients, alveolar macrophages are less activated and produce less hydrogen peroxide in diabetics compared to non-diabetics\(^3\)

Insulin deficiency causes impaired Fc receptor internalization and rats that have been pancreatectomised have deficient Fc-mediated phagocytosis\(^4,5\)

1. Moutschen et al. Diab Metab 1992
3. Wang et al. Tuberc Lung Dis 1999
Global case study: The city of Dhaka, Bangladesh

- ~18.8 million people in Dhaka
- 1/3 of all diabetics living in 48 lowest income countries in the world, are from **Bangladesh**

*A typical morning commute*
Screening Centre network of private clinics/providers in Dhaka

Target population:
~8 million working poor accessing low-cost private clinics

Private clinic in icddr,b network
N= 1,300 physicians or clinics!
• 1 Community Screener at clinic

icddr,b Screening Centre
N= 3
• ~2,200 new TB patients identified annually

Private clinics in icddr,b network:
Mohakhali
Mohammadpur
Golapbagh
In 12 months, **glucometry** in patients: 7,647 underwent testing

832/ 6443 (12.8%) with diabetes among those with **negative Xpert MTB/RIF**

252/ 1204 (20.9%) with diabetes among those with **positive Xpert MTB/RIF**

courtesy Sayera Banu
Diabetics in Indonesia more likely culture positive at 6 months of treatment (22%)

Table 3. Treatment response and outcome of patients with tuberculosis (TB) with and without diabetes mellitus (DM).

<table>
<thead>
<tr>
<th>Period, variable</th>
<th>No. (%) of patients with TB</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With DM (n = 94)</td>
<td>Without DM (n = 540)</td>
<td></td>
</tr>
<tr>
<td>Intensive phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB negative&lt;sup&gt;a&lt;/sup&gt;</td>
<td>67 (71.3)</td>
<td>455 (84.3)</td>
<td>...</td>
</tr>
<tr>
<td>AFB positive</td>
<td>17 (18.1)</td>
<td>54 (10.0)</td>
<td>2.14 (1.17–3.9)</td>
</tr>
<tr>
<td>No sputum sample available, hospital transfer, and/or study default</td>
<td>8 (8.5)</td>
<td>31 (5.7)</td>
<td>...</td>
</tr>
<tr>
<td>Death</td>
<td>2 (2.1)</td>
<td>0 (0)</td>
<td>...</td>
</tr>
<tr>
<td>Culture result positive for <em>Mycobacterium tuberculosis</em></td>
<td>7/41 (17.1)</td>
<td>68/372 (18.3)</td>
<td>0.92 (0.39–2.16)</td>
</tr>
<tr>
<td>End of treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB negative&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70 (74.5)</td>
<td>435 (80.6)</td>
<td>...</td>
</tr>
<tr>
<td>AFB positive</td>
<td>4 (4.3)</td>
<td>17 (3.1)</td>
<td>1.46 (0.48–4.47)</td>
</tr>
<tr>
<td>No sputum sample available, hospital transfer, and or study default</td>
<td>18 (19.1)</td>
<td>88 (16.3)</td>
<td>...</td>
</tr>
<tr>
<td>Death</td>
<td>2 (2.1)</td>
<td>0 (0)</td>
<td>...</td>
</tr>
<tr>
<td>Culture result positive for <em>M. tuberculosis</em>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6/27 (22.2)</td>
<td>32/333 (9.6)</td>
<td>2.69 (1.01–7.14)</td>
</tr>
</tbody>
</table>

NOTE. The intensive phase was the first 2 months of treatment, and end of treatment was at 6 months. AFB, acid-fast bacilli.

- 14.8% prevalence of undiagnosed DM in new TB patients
- TB-DM had greater symptoms at time of diagnosis

Slower culture conversion in diabetics (without cavitary disease)

>20% of diabetics with non-cavitary pulmonary TB remain sputum positive at 3 months of treatment.

Metformin may *reverse* the trends in increased mortality among TB/diabetes

![Graphs showing survival rates with and without metformin usage.]

**Any charted use**

**Used ≥80% time on TB tx**

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**Table 3. Crude and Adjusted Odds Ratios, Based on a Logistic Regression Model, of 2-Month Sputum Culture Positivity for *Mycobacterium tuberculosis* (n = 1323)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crude OR</th>
<th>(95% CI)</th>
<th>PValue</th>
<th>Adjusted OR</th>
<th>(95% CI)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>1.89</td>
<td>(1.40–2.55)</td>
<td>&lt;.001</td>
<td>1.72</td>
<td>(1.25–2.38)</td>
<td>.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>(1.00–1.01)</td>
<td>.510</td>
<td>1.00</td>
<td>(0.99–1.01)</td>
<td>.693</td>
</tr>
<tr>
<td>Male</td>
<td>1.52</td>
<td>(1.10–2.10)</td>
<td>.012</td>
<td>1.43</td>
<td>(0.98–2.08)</td>
<td>.062</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.14</td>
<td>(0.77–1.69)</td>
<td>.510</td>
<td>1.07</td>
<td>(0.70–1.65)</td>
<td>.751</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.90</td>
<td>(0.61–1.34)</td>
<td>.612</td>
<td>0.78</td>
<td>(0.51–1.18)</td>
<td>.242</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>1.55</td>
<td>(0.72–3.33)</td>
<td>.258</td>
<td>1.40</td>
<td>(0.63–3.13)</td>
<td>.410</td>
</tr>
<tr>
<td>History of tobacco use</td>
<td>1.42</td>
<td>(1.06–1.91)</td>
<td>.020</td>
<td>1.05</td>
<td>(0.75–1.48)</td>
<td>.762</td>
</tr>
<tr>
<td>Cavitory disease</td>
<td>4.04</td>
<td>(2.90–5.65)</td>
<td>&lt;.001</td>
<td>4.03</td>
<td>(2.84–5.71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Poor TB treatment adherence</td>
<td>1.06</td>
<td>(0.72–1.57)</td>
<td>.764</td>
<td>1.16</td>
<td>(0.77–1.75)</td>
<td>.490</td>
</tr>
</tbody>
</table>

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Denger et al, Clin Infect Dis 2018
Metformin reduces TB directed tissue pathology and enhances immune response

Singhal et al, Sci Transl Med 2014
Intra-patient pharmacokinetic variability (not non-adherence) predicts response and acquired resistance on anti-TB therapy.
Determinants of anti-TB drug pharmacokinetics:

1. mg/kg dosing (weight categories)
2. poor availability of drug in fixed-dose combinations in some settings or inaccurate quantity of active drug in pill
3. Adherence
4. Age
5. Gender
6. Genetic polymorphism of gut xenobiotic transport
7. Drug interactions
8. Malabsorption
   HIV
   Diabetes
   Cystic Fibrosis
9. Poor solubility

Rifampin exposure significantly reduced in diabetics from Indonesia

(AUC$_{0-6\ h}$), C$_{\text{max}}$ and overall rifampin exposure was 53% lower in diabetics with TB compared to non-diabetics

8-24 mg/L expected $C_{\text{max}}$ range

Java, Indonesia

Diabetics in Virginia were 6.3 times more likely to have slow response (p<0.001) adjusted for age, gender, prior TB episodes, cavitary disease, HIV, alcohol and tobacco use.

Among slow responders, diabetics had significantly lower rifampin levels, measured at the time of estimated peak plasma concentration ($C_{max}$).

Heysell et al. *Emerg Infect Dis* 2010
So to summarize thus far...

Diabetes prevalence will increase in TB endemic countries

Diabetes increases the risk of progression to active TB disease (odds $2.4-8.3$ compared to non-diabetics) and likely higher for poorly controlled diabetics

Treatment outcomes are worse for diabetic TB patients compared to those without diabetes, but may be restored with metformin

Impaired anti-TB pharmacokinetics results in worse in vitro killing of *M. tuberculosis*

Drug concentrations are suboptimal for some diabetic TB patients and may predict in whom dose increase will improve outcome
algorithmic approach in Virginia

HbA1C ≥ 6.5

- Early TDM (at 2 weeks)
- and
- Linkage to DM care

HbA1C <6.5, on diabetes treatment

- Early TDM (at 2 weeks)
- Continue current diabetes regimen

HbA1C <6.5, no prior diabetes

- No intervention (~80% clients)
Practical use of therapeutic drug monitoring (TDM)

- Diabetes
- HIV
- MDR or SLD*

Start treatment

TDM

~2 weeks

Assess Response

~8 weeks

Assess Response

- Slow
- Expected

Further consultation *

Continue DOT

- Slow
- Expected

TDM

*All MDR cases or those needing second-line drugs in Virginia are managed by TB physician consultants
TDM is now programmatic, so timing/procedures are consistent.


Table 3. Dose adjustment for diabetics and HIV/AIDS infected populations

<table>
<thead>
<tr>
<th>Normal drug level</th>
<th>Sub-target INH and Sub-target RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation Phase regimen*</td>
<td>Continue INH 300 mg and RIF 600 mg M-F</td>
</tr>
<tr>
<td>Continuation Phase regimen</td>
<td>Continue INH and RIF M-F or thrice weekly</td>
</tr>
</tbody>
</table>

Recommended dose adjustment for sub-target INH and RIF:
- **Initiation M-F** →
  - INH 300 mg increase to 450 mg
  - RIF 600 mg increase to 900 mg
- **Continuation (M/W/F)** →
  - INH 900 mg
  - RIF 900 mg

*All initiation phase regimens assume target doses of isoniazid (INH) of 5 mg/kg and rifampin (RIF) of 10 mg/kg. M-F= Monday through Friday, 5 x weekly schedule. Sub-target concentrations are any below the expected C2hr range.
CDC Guidelines now provide guidance consistent with VA practice

### Table 9. Conditions or Situations in Which Therapeutic Drug Monitoring May Be Helpful

<table>
<thead>
<tr>
<th>Condition or Situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor response to tuberculosis treatment despite adherence and fully drug-susceptible <em>Mycobacterium tuberculosis</em> strain</td>
</tr>
<tr>
<td>Severe gastrointestinal abnormalities: severe gastroparesis, short bowel syndrome, chronic diarrhea with malabsorption</td>
</tr>
<tr>
<td>Drug–drug interactions</td>
</tr>
<tr>
<td>Impaired renal clearance: renal insufficiency, peritoneal dialysis, critically ill patients on continuous renal replacement</td>
</tr>
<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Treatment using second-line drugs</td>
</tr>
</tbody>
</table>

Abbreviation: HIV, human immunodeficiency virus.

<table>
<thead>
<tr>
<th>Group</th>
<th>Definition</th>
<th>Drugs to check</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - Slow responder (failure to clinically improve as expected)</td>
<td>Clients with smear positive pulmonary TB for a prolonged period of time without improvement (defined as a steady decrease from 4+ to 2+; 3+ to 1+; 2+/1+ to smear negative)</td>
<td>Isoniazid and Rifampin ONLY:</td>
<td>Dose increases in consultation with DTBNH staff and medical consultants. <strong>Follow-up drug levels can be checked.</strong></td>
</tr>
<tr>
<td>2 - All diabetics (HbA1c ≥ 6.5)</td>
<td>Ideally test <strong>2 weeks</strong> after treatment begins. If a recent HbA1c (&lt;3mo) result is not available, perform HbA1c to avoid delaying TDM upon intake. After 8 weeks the window of opportunity is lost so we do not perform TDM (unless slow response or another reason is identified)</td>
<td>Isoniazid and Rifampin ONLY:</td>
<td>Automatic dose adjustment for low level (See Table 2). <strong>No follow-up drug levels checked.</strong></td>
</tr>
<tr>
<td>3 - All HIV positive (regardless of CD4 count or viral load)</td>
<td>Ideally test within <strong>1- 2 weeks</strong> after a stable regimen begins.</td>
<td>Isoniazid and Rifampin/Rifabutin ONLY:</td>
<td>Dose increase in consultation with DTBNH staff. <strong>Follow-up drug levels can be checked.</strong></td>
</tr>
<tr>
<td>4 - Others</td>
<td>Other scenarios in discussion with TB consultants (e.g., new clinical deterioration, receiving second-line TB medications, sudden relapse, severe illness, other co-morbidities)</td>
<td>Case-by-case</td>
<td>Case-by-case</td>
</tr>
</tbody>
</table>
Concentrations increase after dose adjustment

**Vancouver**

\[ A \]
\[ B \]

**Figure** Serum response per 100 mg increase in dosage.  
A. Serum isoniazid levels, \( n = 17 \).  
B. Serum rifampicin levels, \( n = 9 \).

**Virginia**

B.  

van Tongeren, *IJTLD* 2013

*(similar overall mean increase)*

Heysell, *Emerg Infect Dis* 2010
Diabetes (with early TDM) in 2013-14 trend toward faster sputum culture conversion compared to matched* non-diabetes, but not in 2009-10 (without early TDM)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Matched 2009-2010</th>
<th>Matched 2013-14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>non DM N=60</td>
<td>DM N=30</td>
</tr>
<tr>
<td>culture conv (days ±SD)</td>
<td>57±35</td>
<td>61±32</td>
</tr>
<tr>
<td>2 months culture conv (%N)</td>
<td>34 (57)</td>
<td>15 (50)</td>
</tr>
</tbody>
</table>

Difference most apparent in diabetes (2009-2010) matched to diabetes (2013-2014)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>2009-10 N=26</th>
<th>2013-14 N=26</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>culture conv (days ±SD)</td>
<td>62±31</td>
<td>42±22</td>
<td>0.01</td>
</tr>
<tr>
<td>2 months culture conv (%N)</td>
<td>13(50)</td>
<td>21(81)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*matched for age (10 yrs), gender, smear status (pos or neg), CXR (cavity or not)
Other early interventions were taking place with therapeutic drug monitoring

- Were other interventions responsible for diabetes patients improved culture conversion?
  - Nurse-patient educational flipchart
  - **metformin** (autophagy)

Patients diagnosed with TB in Virginia now receive hemoglobin A1c testing:
212 patients treated for TB in 2016
→ 2-3% are new diabetes diagnosis, primarily for triage to diabetes care
Local case: Unmasked MDR, missed opportunity for early TDM?

23 y/o man originally from the Philippines

Presented with R neck mass (lymphadenopathy), voice change

HIV + (CD4 124)

Sputum and R neck biopsy → smear (4+ from sputum) and culture positive for M. tuberculosis

Interestingly CXR was normal (laryngeal TB?)

Pretreatment Mtb isolate: embB L355L (silent) embB G378A (neutral)

4 month treatment isolate: embB L355L (silent) embB G378A (neutral)

inhA C-15T → R by MGIT
rpoB D518Q → R by MGIT

TDM C2hr: INH low and RIF very low

RIPE Atripla → RI only → MDR regimen

months symptoms
1 2 3 4 5 6

Xpert rpoB wildtype
MGIT SIRE +PZA (pansusceptible)

Smear negative, late growth cx positive:
MDDR (CDC) → INH R and RIF R
Simplifying sample collection, preparation and analysis

Current approach

Urine instead of blood draw

HPLC/ mass spec

Spectrophotometric

Colorimetric/ mobile phone

NIH R01 to Rutgers and University of Virginia
“That tuberculosis and diabetes represent two of the greatest global health challenges of our time, and their convergence globally represents a looming co-epidemic,

That this looming co-epidemic threatens progress against TB,

That, based on what we have learned from past co-epidemics, particularly TB-HIV, we must act early and decisively to avoid large numbers of avoidable deaths”
Thank you!

All the Nurses/Case Managers
Denise Dodge
Deborah Staley
Jane Moore (retired)
Suzanne Keller (retired)

Yusra Alkabab
Tania Thomas
Eric Houpt

Sayera Banu
Shahriar Ahmed
Kishor Kumar Paul
Sara Sabrina Ferdous
S.M. Mazidur Rahman
The case of the 90 y/o man with MDR-TB

- 90 year-old man, originally from Peru
- Came to live in the U.S. in November of 2014
- He is healthy, active and asymptomatic. No prior history of TB.
- A skin test is performed because his daughter operates a child-care facility from their home → skin test positive
- CXR → “upper lobe infiltrate with pleural thickening, no cavity”

June 5, 2015 → smear negative, culture negative
June 6, 2015 → smear negative, culture positive (MTb complex)
June 7, 2015 → smear negative, culture positive (MTb complex)

July 1, 2015 → starts treatment with rifampin, isoniazid, pyrazinamide, ethambutol but isolate ultimately found to be MDR (by MGIT SIRE)........
These DST results return

\[ \text{rpoB} \rightarrow \text{mutated} \ (\text{Ser531Leu}) \]
\[ \text{katG} \rightarrow \text{mutated} \ (\text{Ser315Thr}) \]
\[ \text{inhA} \rightarrow \text{no mutation} \]
\[ \text{embB} \rightarrow \text{mutated} \ (\text{Met306Iso}) \]
\[ \text{pncA} \rightarrow \text{no mutation} \]
\[ \text{gyrA} \rightarrow \text{no mutation} \]
\[ \text{gyrB} \rightarrow \text{no mutation} \]
\[ \text{rrs} \rightarrow \text{no mutation} \]
\[ \text{tlyA} \rightarrow \text{no mutation} \]
\[ \text{eis} \rightarrow \text{mutated} \ (G-37T) \]

Rifampin (1.0 \(\mu\text{g/ml}\)) \(\rightarrow\) \text{R} \ [\text{rifabutin} \rightarrow \text{R}]
Isoniazid (1.0 \(\mu\text{g/ml}\)) \(\rightarrow\) \text{R}
Ethionamide (10.0 \(\mu\text{g/ml}\)) \(\rightarrow\) \text{R}
Ethambutol (5.0 \(\mu\text{g/ml}\)) \(\rightarrow\) \text{R}
Pyrazinamide (100 \(\mu\text{g/ml}\)) MGIT 960 \(\rightarrow\) \text{S}

Ofloxacin (2.0 \(\mu\text{g/ml}\)) \(\rightarrow\) \text{S}

Amikacin (4.0 \(\mu\text{g/ml}\)) \(\rightarrow\) \text{S}
Capreomycin (10.0 \(\mu\text{g/ml}\)) \(\rightarrow\) \text{S}
Kanamycin (5.0 \(\mu\text{g/ml}\)) \(\rightarrow\) \text{R}

Also: PAS (2.0 \(\mu\text{g/ml}\)) \(\rightarrow\) \text{S}
Streptomycin 2.0 \(\mu\text{g/ml}\) \(\rightarrow\) \text{S}
Streptomycin 10.0 \(\mu\text{g/ml}\) \(\rightarrow\) \text{R}

Creatinine Clearance = 44 mL/min
A range of treatment approaches → this is *individualized* care

Levofloxacin (better tolerated?) → 250 mg daily but *TDM*

Pyrazinamide (continue wt based) → 1500 mg daily but *TDM* given high cost of failure

PAS (given other resistance patterns, avoid cycloserine) → 2 g po bid and *TDM*

Linezolid (low dose given toxicities) → 300 mg daily but *TDM* given reports of acquired resistance with lower dose

→ Obtain *MICs* including cycloserine DST and clofazimine, linezolid, bedaquiline

→ Consider adding clofazimine or substitution for other oral if intolerance or toxicity

→ Hold on amikacin or capreomycin for now
# TDM/ MIC to optimize dose and minimize toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutation</th>
<th>APM</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>katG</td>
<td>R</td>
<td>R (2)</td>
</tr>
<tr>
<td>RIF</td>
<td>rpoB</td>
<td>R</td>
<td>R (&gt;4)</td>
</tr>
<tr>
<td>EMB</td>
<td>embB</td>
<td>R</td>
<td>R (8)</td>
</tr>
<tr>
<td>PZA</td>
<td></td>
<td>S</td>
<td>(MGIT)</td>
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<tr>
<td>STR</td>
<td></td>
<td>R</td>
<td></td>
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<tr>
<td>CAP</td>
<td></td>
<td>S</td>
<td>S (2)</td>
</tr>
<tr>
<td>KAN</td>
<td>eis G-37T</td>
<td>R</td>
<td>R (16)</td>
</tr>
<tr>
<td>AMK</td>
<td></td>
<td>S</td>
<td>S (2)</td>
</tr>
<tr>
<td>OFLOX</td>
<td></td>
<td>S</td>
<td>S (1)</td>
</tr>
<tr>
<td>LEVO</td>
<td></td>
<td>S</td>
<td>(0.5)</td>
</tr>
<tr>
<td>MOXI</td>
<td></td>
<td>S</td>
<td>(0.25)</td>
</tr>
<tr>
<td>PAS</td>
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<td>S</td>
<td>(0.25)</td>
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<tr>
<td>ETO</td>
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<td>R</td>
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<td>S</td>
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<tr>
<td>LZD</td>
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<td>S</td>
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</tr>
<tr>
<td>CFZ</td>
<td></td>
<td>S</td>
<td>(0.06)</td>
</tr>
<tr>
<td>BDQ</td>
<td></td>
<td>S</td>
<td>(0.06)</td>
</tr>
</tbody>
</table>

MIC testing: CDC and National Jewish Health

**Pyrazinamide** 1500 mg daily
C2hr- **36.59** (expected C2hr: 20-60 µg/ml)
C6hr- 24.62

**Levofloxacin** 250 mg daily
C2hr- **4.71** (expected peak: 8-12 µg/ml)
C6hr- 2.54

Levofloxacin 500 mg daily
C2hr- **5.83**

**PAS** 2g bid
C6hr- **4.98** (expected C4-6hr: 20-60 µg/ml)

PAS 4g bid
C6hr- **46.77**

**Linezolid** 300 mg daily
trough –trace (expected for daily dose)
C2hr- **6.41** (expected peak: 12-26 µg/ml)

Linezolid 600 mg daily
C2hr- **14.03**