TB Special Situations
Case Discussions

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Special Situations

- Diabetes
- Pregnancy
- Hepatic Disease
- Advanced Age
- Renal Disease
Case 1

55 yo diabetic M, presents with cough, hemoptysis, weight loss x 3 months

55 yo diabetic M

- On three different oral DM medications
- HbA1c=10%
- Smear positive x 3, numerous
- GeneXpert- MTBC detected, rifampin resistance detected
- Next steps?
Diabetes + TB

❖ Patients with risk factors for DM should be screened with fasting glucose or HbA1c
  - ADA risk factors include: Age >45, BMI >25, first-degree relative with DM, and race/ethnicity (African American, Asian, Hispanic, American Indian/Alaska Native, or Hawaiian Native/Pacific Islander)

Diabetes + TB

❖ Drug-drug interactions
  - Sulfonylureas- RIF decreases concentration
  - Thiazolidinedione- RIF decreases concentration
  - Dipeptidyl peptidase inhibitor- RIF decreases concentration
  - Rifampin alone has been associated with hyper/hypoglycemia in DM and non-DM patients
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<tbody>
<tr>
<td>Rifampicin and Anti-Diabetic Agents</td>
<td>Glucose homeostasis</td>
<td>24 hours from the last dose</td>
<td>No special considerations</td>
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<tr>
<td>Metformin</td>
<td>Glucose homeostasis</td>
<td>24 hours from the last dose</td>
<td>No special considerations</td>
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<tr>
<td>Sulfonylureas (e.g., Glipizide)</td>
<td>Glucose homeostasis</td>
<td>24 hours from the last dose</td>
<td>No special considerations</td>
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<tr>
<td>Thiazolidinediones (e.g., Rosiglitazone)</td>
<td>Glucose homeostasis</td>
<td>24 hours from the last dose</td>
<td>No special considerations</td>
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<tr>
<td>Glitazones (e.g., Pioglitazone)</td>
<td>Glucose homeostasis</td>
<td>24 hours from the last dose</td>
<td>No special considerations</td>
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<tr>
<td>Insulin analogues (e.g., Glargine)</td>
<td>Glucose homeostasis</td>
<td>24 hours from the last dose</td>
<td>No special considerations</td>
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**Additional Information:**
- Rifampicin may decrease the effectiveness of oral antidiabetic drugs. Patients should be monitored closely and their antidiabetic dose may need to be increased.
- Glucosidase inhibitors may cause hypoglycemia when used with rifampicin.
- The combination of rifampicin and metformin may result in increased metformin excretion and decreased blood levels of metformin.
- Thiazolidinediones may increase the risk of hypoglycemia when used with rifampicin.
- Glitazones may increase the risk of hypoglycemia in patients taking rifampicin.

**Precautions:**
- Patients should be monitored closely for signs of hypoglycemia.
- Dose adjustments may be necessary for both rifampicin and the antidiabetic agent.
- Regular monitoring of blood glucose levels is recommended.

**References:**
- Guidelines for the management of diabetes mellitus.
- Antidiabetic agents: a review of their use in the management of type 2 diabetes mellitus.
Diabetes + TB

<table>
<thead>
<tr>
<th>Factors</th>
<th>Evidence</th>
<th>References</th>
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<tbody>
<tr>
<td>Increased risk of progression to TB (Relative risk of progression to active TB 2-4.1)</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Higher treatment failure</td>
<td>++/-</td>
<td></td>
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<tr>
<td>Increased risk of drug-resistant TB</td>
<td>+/-</td>
<td>Jimenez-Corona, Thorax, 2013</td>
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Radiographic presentation may vary, but studies are mixed:

- More cavities
- Lower lung involvement

55 yo diabetic M

- PSQ with no INH mutations detected; presence of RIF resistance
- DST confirms rifampin mono-resistance
- RIF d/c'd, unable to tolerate PZA. Multiple med re-challenge due to GI side effects
- Complains of pill burden and ongoing GI distress
- Blood sugars 300-400
- Eventually on stable regimen of INH/EMB/FQ/injectable
- Remained numerous smear positive through month 2
- Next steps?

Diabetes- length of TB treatment

- Patients with DM and either cavitation on initial CXR OR positive culture at 2 months should be followed more closely with consideration to extend treatment.
- Some experts recommend extending treatment to 9 months in poorly controlled DM.

Diabetes- treatment may be more difficult

- Peripheral neuropathy
- Diabetic Gastroparesis
- Diabetic retinopathy
- CKD
- Drug-drug interactions
- Rifampin increases intestinal absorption of glucose

Therapeutic drug monitoring (TDM)

- Controversial
  - Unclear clinical significance in all-comers- reports of both no impact vs poor outcome on treatment cure/relapse
  - Typically peak levels drawn (2-3 hours post-dose), with later level (6 hours) if delayed absorption is suspected refer to the drug guide
  - Samples need prompt processing (INH, ethionamide are unstable at room temp in whole blood/serum, followed by RIF, rest likely stable x 24 hours)

Therapeutic drug monitoring (TDM)

When might this be helpful?
- Poor response to MTB treatment (radiographic, microbiologic, or clinical)
- GI issues or suspected absorption issues (e.g. chronic diarrhea, gastroparesis, short bowel syndrome, IBD)
- Kidney disease (e.g. CKD, PD, CRRT)
- Drug-Drug Interactions (e.g. ART)
- Diabetes
- 2nd line drugs


Case 2

25 yo Chinese G1P0, PPD+
25 yo pregnant F

- CXR- “left apical nodularity, scarring and volume loss which likely represent sequelae of old granulomatous disease. Recommend correlation with prior imaging.”
- Immigrated from China in 2013
- Chronic cough x month. Sore throat and hoarseness x 1 week.
- 36 weeks pregnant
- Next steps?

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25 yo pregnant F

- Repeat CXR- “unchanged left apical scarring consistent with sequelae of prior granulomatous disease”
- Sputum- numerous smear positive (x3)
- GeneXpert- MTBC detected, no rifampin resistance detected
- Next steps?
25 yo pregnant F

- Sputum- numerous smear positive
- GeneXpert- MTBC detected, no rifampin resistance detected
- CT- “left apical scarring with bronchiectasis and calcification, likely sequelae of prior granulomatous disease” (done after delivery)
- Next steps?

Pregnancy

- Pregnancy does not increase the risk for progression to active TB
- Routine screening not indicated unless high risk for infection (e.g. FB) or progression (e.g. recent contact, immunosuppressed)
- However, if screening is positive, CXR indicated as soon as possible. Abnormal CXR should have expedited evaluations
- Monitoring
  - LFT baseline and ongoing monitoring due to risk for hepatotoxicity, likely highest in 3rd trimester and 1st 3 months post-partum
  - Frequent sputums to assess infectiousness

Pregnancy - treatment

- PZA is controversial in the US due to lack of safety data
  - More strongly considered if HIV+, extrapulmonary, severe TB, drug-resistant
  - WHO* and IUATLD recommends all 4 drugs
  - Some experts recommend all 4 drugs based on above and the fact that PZA has been used for years in high endemic countries
- All 4 first-line drugs are category C
- Administer pyridoxine given risk for neuropathy
- Aminoglycosides with known teratogenicity. Use of 2nd line agents- seek consultation
- Duration of treatment is the same as in non-pregnant pan-susceptible disease


25 yo pregnant F, 37 weeks

- Patient was started on RIPE
- 1 week f/u: tolerating meds, LFT normal
- Home contacts include- 3 adults + 3 kids
- She participated in 3-hour pre-natal classes
- Next steps?
Contact evaluation and Infection Control

- Home
- Outpatient OB clinic
- Inpatient delivery plan
  - Mother
    - Determination of isolation procedures - pre/peri/post
    - Placenta for path and culture
  - Baby
    - Evaluation for congenital TB
      - Physical exam - fever, irritability, HSM, LAD, cough, poor feeding
      - CXR
    - If concerns for congenital TB: gastric aspirates, LP, sepsis w/u, start RIPE
    - Decision of window prophylaxis if congenital TB work-up negative

25 yo pregnant F, 39 weeks

- Household contacts 1<sup>st</sup> test negative
- 4/10 outpatient OB providers TST neg
- Mom admitted for induction due to oligohydramnios
- Smear neg x 1
- Next steps?
Baby evaluation

- Evidence of chorioamnionitis
- Baby required minimal Bipap/cpap due to stunning
- Initially started on window proph, then expanded to RIPE after sleepiness, hypoglycemia, and temp instability
- Started on amp/gent
- LP unremarkable
- Gastric aspirates done
- Mother: Smear neg x 3
- Next steps?
Breastfeeding

Small concentrations of TB medications (not enough to provide treatment) are detected in breast milk and have not been reported to cause toxicity to the nursing infant.

Thus, breastfeeding is encouraged in non-infectious women on 1st line medications.

Exclusively breast-fed infants should receive supplementary pyridoxine (1-2 mg/kg/day).

Case 3

44 yo Korean M, immigration evaluation
Screening labs include:
- HBV sAg positive, sAb negative
- HIV neg, HbA1c 6%
- LFT normal, INR normal
- Asymptomatic
- Sputum smear positive
- GeneXpert- MTBC detected, no rifampin resistance detected

Next steps?

You provide counseling and the patient has never been given a diagnosis of hepatitis B.

Due to smear positivity, liver imaging will be delayed

Patient does not have a PCP or insurance due to new immigration status.

Next steps?
When do you consider an alternate regimen?

- ALT >3x ULN at baseline, not due to TB
- Prior history of hepatotoxicity to TB meds
- Advanced liver disease, e.g. cirrhosis/ESLD
  - By ultrasound or CT
  - By markers of end-stage liver disease (ESLD): INR, bilirubin, AST/ALT, bilirubin
- Consider liver-sparing regimen

Drug-induced Liver Injury (DILI)

- Causative:
  - PZA (1%)
  - INH
    - Asymptomatic elevation <5x ULN in 10-20%
    - Clinical hepatitis, 0.1-2.7% depending on combo
    - Fatal hepatitis <0.023%
  - RIF
    - rare except in combination with other drugs
    - Asymptomatic hyperbilirubinemia (0.6%)
    - Cholestatic pattern of hepatitis
44 yo Korean immigrant with chronic HBV

- RIPE is started
- 1 week later: AST 80, ALT 120 (asymptomatic)
- 2 weeks later: AST 250, ALT 300 (fatigue)
- Next steps?

DILI (management)

- HOLD medications for the following or any GI complaint: abdominal pain, diarrhea, fatigue, nausea/vomiting, anorexia, malaise, jaundice, dark urine.
- Check LFT’s
- If LFT <5x upper limit of normal (ULN) and asymptomatic, okay to restart but may need closer monitoring.
- If LFT <3x ULN and symptomatic, okay to restart with supportive measures, e.g. treatment of gastritis or nausea. May need closer monitoring.
DILI (management)

❖ STOP medications for the following:
  ❖ Asymptomatic + LFT >5x upper limit of normal (ULN)
  ❖ Symptomatic + LFT >3x ULN
  ❖ Screen for hepatitis (A, B, C) or other underlying causes of liver
disease (alcohol use, other hepatotoxic medications). Check INR.
  ❖ Determine if urgent evaluation or admission is needed (e.g. >10x
ULN or any evidence of liver failure- asterixis, confusion,
dehydration, coagulopathy)

44 yo Korean immigrant with chronic HBV, AST/ALT rise

❖ Meds are held
❖ Med list reviewed- none
❖ No ETOH reported
❖ Liver US- unremarkable
❖ 1 week follow-up: symptoms resolved and AST/ALT 50/40
❖ Smears are still positive
❖ Next steps?
DILI (re-challenge)

- Monitor LFTs weekly until 2x ULN (some programs completely normal), before re-challenging with medications. If severe TB disease, may need to start liver-sparing regimen.

- Seek consultation in re-introduction of medications.

- Choice in med re-challenge depends on co-morbidities (cirrhosis), degree of hepatitis (mild vs severe), susceptibilities (pan-susceptible or pending), phase (initial or continuation), and most likely suspect (PZA/INH>RIF).

- Typically, start least suspect agent first (along w/ non-hepatotoxic meds), monitor LFTs in 3-7 days, and if remain normal then re-challenge with next agent.

44 yo Korean immigrant with chronic HBV, AST/ALT rise

- EMB restarted

- 3 days later, AST/ALT normal and rifampin restarted

- 1 week later, AST/ALT normal and INH restarted

- 1 week later, AST/ALT are 180/150 with nausea

- Next steps? What would be your potential alternate regimens?
Hepatic Disease

Most likely hepatotoxic medications: PZA, INH >> RIF

<table>
<thead>
<tr>
<th>If you avoid…</th>
<th>Alternate treatment</th>
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<tbody>
<tr>
<td>PZA</td>
<td>RIF + INH + EMB x 2 months, followed by 7 mo RIF + INH</td>
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<tr>
<td>INH + PZA</td>
<td>RIF + EMB + FQ/injectable/cycloserine x 12-18 mo</td>
</tr>
<tr>
<td>INH</td>
<td>RIF + PZA + EMB x 6 mo</td>
</tr>
<tr>
<td>INH + PZA + RIF</td>
<td>EMB + FQ + cycloserine +/- injectable x 18-24 mo</td>
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<tr>
<td>Little to no potential of DILI</td>
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Case 4

96 yo Indian F diagnosed with pulmonary TB
96 yo F with pulm TB

- Numerous smear positive disease
- CXR- RUL cavity
- Weight 85 lbs
- Creatinine 1.0
- How do you proceed?

Advanced Age

- Risk of DILI (drug-induced liver injury) increases with age
- Some experts avoid PZA in pts >75 yo
- Risk / benefit decisions on RIPE vs RIE vs RIE+FQ
  - Consider severity of disease and bacillary load
  - Consider risk for drug resistance
  - Consider risk for DILI
- Close medication review due to drug-drug interactions needed

Advanced Age

Low BMI / malnutrition is often an issue:
- Close monitoring of weight and dose adjustments
- May need nutritional supplementation

Creatinine may not accurately reflect actual CrCl/GFR due to low muscle mass. Calculation recommended.

Close medication review needed due to drug-drug interactions and an ever-changing polypharmaceutical list (often includes anti-HTN, thyroid replacement, antidepressants, and blood thinners)

Associated with higher mortality and poor outcomes.


96 yo F with pulm TB - back to the case

Calculated CrCl~19.9

She has a history of PE on coumadin, HTN, DM

In addition, you find out that she lives at home with her daughter, son-in-law, and 4 grandchildren (ages 6 months, 4 yo, 7 yo, 10 yo)

GeneXpert- MTBC detected, rifampin resistance not detected

How do you proceed?
Renal Disease

<table>
<thead>
<tr>
<th>Requires dose / frequency adjustment</th>
<th>No adjustment</th>
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<tbody>
<tr>
<td>Pyrazinamide- 25-35 mg/kg TIW</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Ethambutol- 20-25 mg/kg TIW</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Levofloxacin- 750-1000 mg TIW</td>
<td>Moxifloxacin</td>
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</table>

❖ All TB medications should be ideally given after HD on HD days.
❖ Consider monitoring drug levels
❖ PD- no data available


96 yo F with pulm TB- discussion points

❖ EMB/PZA should be renally dosed
❖ Consideration of drug-drug interactions- ?use rifabutin vs discuss with PCP need for interacting medications
❖ Risk / benefit discussion regarding 4 drugs- heavy burden of disease + high risk contacts at home vs. DDI and potential for toxicity
❖ Consider nutrition status and how to improve
Assistance is right around the corner…

- CITC warmline: 877-390-6682 (toll-free)
- Your friendly neighborhood TB controller
- Turn around to those sitting next to you in the room