Adverse Drug Reactions

John Zeuli, PharmD, BCPS
Department of Pharmacy
Mayo Clinic, Rochester  MN
Disclosures

• I have no relevant financial disclosures

• Off-label discussion:
  • I will refer to antibiotics used for the treatment of tuberculosis that may not have FDA approval for the treatment of tuberculosis
Objectives

1. Describe the common adverse reactions to TB treatment regimens
2. Explain how to manage adverse reactions to TB treatment regimens
## Duration of Tuberculosis Treatment

<table>
<thead>
<tr>
<th>Drug-Susceptible</th>
<th>MDR</th>
<th>XDR</th>
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<tbody>
<tr>
<td>First-line drugs</td>
<td>2nd and 3rd Line drugs</td>
<td>2nd and 3rd Line drugs</td>
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<tr>
<td>INH/RIF/EMB/PZA X 2 months</td>
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<td>INH/RIF X 4 months</td>
<td>More toxicity</td>
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<td>18+ months</td>
<td>24+ months</td>
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<td>Consider surgery</td>
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**Drug-Susceptible**
- First-line drugs: INH/RIF/EMB/PZA X 2 months
- INH/RIF X 4 months

**MDR**
- 2nd and 3rd Line drugs
- A minimum of 4 (preferably 5 or 6) active drugs
- More toxicity
- 18+ months

**XDR**
- 2nd and 3rd Line drugs
- A minimum of 4 (preferably 5 or 6) active drugs
- More toxicity
- 24+ months
- Consider surgery
Adverse Events During Treatment of TB

• Very common
  • More than 80% of patients on treatment for DR-TB will have adverse events

• Even mild and common events can affect treatment outcomes

• Some adverse events can be life-threatening

• Some adverse events can cause permanent disability

• Critical drugs may be discarded if not properly addressed

• Timely recognition and management of adverse events important for adherence and completion of treatment
Potency and Tolerability of TB Drugs

Increasing potency, reliability, reproducibility of susceptibility testing

First-line Drugs
- Rifampin
- Isoniazid
- Pyrazinamide
- Ethambutol

Fluoroquinolones
(moxifloxacin, gatifloxacin, levofloxacin)

Injectable agents
Aminoglycosides (streptomycin, amikacin, kanamycin)
Polypeptides (capreomycin)

Oral bacteriostatic agents
(ethionamide, prothionamide, cycloserine/terizidone, p-aminosalicylic acid, thiacetazone)

Agents with unclear efficacy (clofazimine, amoxicillin-clavulanate, clarithromycin, linezolid)

Second-line Drugs

Decreasing tolerability

Lecture layout

- 2 sections
  - 1\textsuperscript{st} line therapy
  - 2\textsuperscript{nd} line therapy
- Cases to highlight key adverse effect management
- Discussion of adverse effect management
- Drug Adverse Effect monographs woven in
- Section recap/summary
General Approach

- Managing Reaction
- Resuming Treatment
- Educating Patients
- Prevention
- Early Identification
- Systematic Evaluation
- Isolation Cause
Confounding the Picture
Hepatotoxicity Case 1

• 43 yo male started on INH, RMP, PZA, and EMB. Baseline AST/ALT/Bilirubins were WNL. After 4 weeks of therapy, his lab results show the following:
  • AST: 284 U/L (8-48 U/L)
  • ALT: 164 U/L (7-55 U/L)
  • Bili-T: 1.1 mg/dL (0.1 -1.0mg/dL)
  • Bili-D: 0.2 mg/dL (0.0 – 0.3 mg/dL)

• How would you manage this situation?
TB medications-Hepatotoxicity

- INH + RMP → INH → PZA → Rif → Ethionamide
TB drug hepatotoxicity management

1) Rule out/address other causes/confounders
   a. hepatotoxic drugs, acute hepatitis, alcohol, etc.

2) Does the patient have symptoms?
   S/S: Nausea/vomiting with anorexia, abdominal tenderness, jaundice, rib discomfort-R upper abdomen, hepatic enlargement
   a. Yes, Stop all meds!
   b. No:
      i. <3-5x ULN, Continue program with symptom monitoring. (Re-assess PZA need)
      ii. >3-5x ULN, hold therapy until AST/ALT return to baseline and then serial reintroduction
Hepatotoxicity management

• Symptomatic/Transaminase elevations >3-5x ULN
  • Hold all medications
  • When symptoms resolve and LFTs are in normal range, consider drug re-introduction in stepwise fashion every 4 days
    • EMB x 3 days
    • EMB/Rifampin x 3 days
    • EMB/Rifampin/INH x 3 days
    • PZA addition/evaluation
      • EMB/INH/Rifampin/PZA (close LFT monitoring)
      • EMB/INH/Rifampin (extended duration)

• If symptoms recur or AST/ALT increase upon re-challenge, then d/c drug cause, substitute another drug, and adjust treatment duration as needed
Hepatotoxicity case 1

• Confounders: drinking 3-4 glasses of wine in the evening 4-5 nights weekly
• Symptoms: Asymptomatic
• LFTs ~3-5x ULN, AST/ALT ratio 2:1
• Management???
  • Alcohol ceased
  • TB therapy continued
  • Labs at 1 week after alcohol cessation:
    • AST: 83 U/L (8-48 U/L)
    • ALT: 52 U/L (7-55 U/L)
Hepatotoxicity case 2

• 36 yo female started on INH, RMP, PZA, and EMB. Baseline AST/ALT/Bilirubins were WNL. After 4 weeks of therapy, her lab results show the following:
  • AST: **143** U/L (8-48 U/L)
  • ALT: **182** U/L (7-55 U/L)
  • Bili-T: 0.9 mg/dL (0.1 –1.0mg/dL)
  • Bili-D: 0.2 mg/dL (0.0 – 0.3 mg/dL)
Hepatotoxicity case 2

- Confounders: Occasional alcohol, acetaminophen use
- Symptoms: Asymptomatic
- LFTs ~3-5x ULN

Management???

- Educate on alcohol/acetaminophen
- TB therapy continued
- Labs at 2 months after alcohol cessation:
  - AST: 124 U/L (8-48 U/L); ALT: 162 U/L (7-55 U/L)
- Labs at 3 months (PZA stopped):
  - AST: 62 U/L (8-48 U/L); ALT: 82 U/L (7-55 U/L)

Patient successfully completed 6 months of therapy with cure
Hepatotoxicity case 3

- 58 yo male started on INH, RMP, PZA, and EMB. Baseline AST/ALT/Bilirubins were WNL. After 4 weeks of therapy, lab results show the following:
  - AST: 264 U/L (8-48 U/L)
  - ALT: 316 U/L (7-55 U/L)
  - Bili-T: 0.9 mg/dL (0.1 -1.0 mg/dL)
  - Bili-D: 0.2 mg/dL (0.0 – 0.3 mg/dL)
Hepatotoxicity case 3

- Confounders: alcohol 2-3x week, NASH, acetaminophen use twice daily, atorvastatin 40mg (primary ppx)
- Symptoms: Asymptomatic
- LFTs >5x ULN
- Management???
  - Cease alcohol/acetaminophen/atorvastatin
  - TB therapy ceased
  - Labs at 1 week:
    - AST: 140 U/L (8-48 U/L); ALT: 110 U/L (7-55 U/L)
Hepatotoxicity Case 3

• **Management???
  • Continued hold of TB therapy
  • Labs at 2 weeks:
    • AST: 48 U/L (8-48 U/L); ALT: 62 U/L (7-55 U/L)
  • Sequential tapered drug reintroduction:
    • EMB/Rifampin x 3 days (LFTs WNL)
    • EMB/Rifampin/INH x 3 days (LFTs 1.5-2x ULN)
    • PZA addition/evaluation
      • EMB/INH/Rifampin/PZA (close LFT monitoring)
      • EMB/INH/Rifampin (extended duration)
Isoniazid (INH) – Adverse reactions

- **Hepatotoxicity / hepatitis**
  - Usually seen in 1st 4-8 weeks of therapy
  - Transient *asymptomatic elevation* of AST/ALT in 10-15%
  - *Rapid improvement* (AST/ALT) after stopping drugs - clue to INH toxicity

- **Peripheral neuropathy**
  - give vitamin B6 (25-50 mg/d) to at risk patients

- **Other:**
  - Rash
  - Hypersensitivity – (+) ANA (< 20%); lupus-like reaction (<10%)
  - Tyramine rxn
  - optic neuropathy (rare)
  - **CNS** - toxic psychosis, behavioral changes, seizure / gen. convulsions
Rifampin Cases
R-case 1

- 64 yo female started on INH, RMP, PZA, and EMB. Baseline labs were WNL. After 3 weeks of therapy, she reports intermittent headaches vision. BP **178/94** (baseline 130s/70s).
  - Other Med list:
    - Calcium carbonate 500mg daily, amlodipine 10mg daily, doxazosin 8mg nightly, metoprolol succinate 150mg daily

- Management thoughts?
Rifampin

- Primary adverse effect = effect on other medications!
- Potent CYP 3A, CYP 2C, and PgP inducer
- Careful review of medication list prior to starting
- Empiric adjustment/med change often warranted
- Rifabutin less potent, can often be substituted
R-case 1

• Pt med list:
  • Calcium carbonate 500mg daily, **amlodipine** 10mg daily, **doxazosin** 8mg nightly, **metoprolol succinate** 150mg daily

• Management thoughts?
  • Amlodipine, metoprolol, and doxazosin levels dramatically reduced in presence of Rifampin
  • Low anti-hypertensive levels = symptomatic hypertension
  • Increase doses, adjust/add/modify antihypertensive therapy, monitor accordingly
R case 2

• 19 yo female nursing student started on Rifampin for 4 month course of LTBI treatment.
  • PMH: quarterly migraines, respond to ibuprofen, acetaminophen, promethazine
  • Reports no other medications, but claims she is on oral birth control upon interview
  • Thoughts?
R case 2

• Rifamycin primary adverse effect = effect on other medications!

• Oral contraceptives = progestin +/- estrogen
  • Both hormones metabolized via CYP3A4
  • Rifampin lowers levels
  • Backup method until 4 weeks after completion of rifampin
Rifampin – Adverse reactions

• **Drug interactions** - induces Cyt. P450 system and will _decrease_ levels of (sampling):
  - Steroids
  - OCPs
  - Coumadin
  - Methadone
  - Digoxin
  - Alpha blockers
  - Azoles
  - CCBs

• **Orange discoloration** of body fluids; stains soft contact lenses
  - Not a toxicity; this is expected

• Hepatotoxicity / hepatitis (↑bilirubin is a clue to RFP toxicity; ↑AST/ALT)
• Cytopenias - ↓WBC, ↓Plts (*bleeding problems)
• Influenza-like syndrome
• Hypersensitivity reactions (lupus-like reactions can occur with rifamycins)
Rash
Rash Case 1

• 54 yo male started on INH, RMP, PZA, and EMB. Baseline labs were WNL. After 2 weeks of therapy, he reports a rash on his chest.

• How should we manage?
Confounding the Picture
Rash Case 1

• **Scenario 1:** After interview you find, he changed his laundry detergent the day prior to the rash and started a new supplement from Korea (provided by a close friend) to boost his mood.

• **Management:**
  1. symptomatic treatment: topical corticosteroid/oral antihistamine
  2. cessation of supplement
  3. reversion to prior laundry detergent

• Rash gone after 3 days
Rash Case 1

• **Scenario 2**: No confounders/alternative explanation identified

• Management??
Rash Assessment

- Severe cutaneous reactions = rare
  - Idiosyncratic, Inpatient management, derm consult, biopsy, reintroduction of meds in managed setting, challenging to identify culprit drug, desensitization
- Maculopapular rash/Itching = much more common
  - Reported with all 1st line TB drugs
  - Typically develop early (during first few weeks of therapy)
  - May resolve with cautious continuation of all medications
  - Mild skin lesions /symptoms: Consider continuation
  - Moderate reaction/symptoms: Can stop drug therapy
Rash Management

1. **Assessment of rash**
   a) **Severe vs mild-moderate**
      1. **Severe** = anaphylaxis, angioedema, SJS, TEN, etc.
      2. **Concerning symptoms:**
         Fever, rapid spreading, large body surface area, mucous membrane involvement, throat swelling

2. **Determine need to cease medications**
   - **Severe** = cease medications
   - **Moderate** = usually cease medications
   - **Mild** = often continue medications

3. **Treat symptoms** (antihistamine, topical corticosteroid, leukotriene inhibitor)

4. **TB med reintroduction/substitution as appropriate**
Med reintroduction after rash

1. Start potent, long-acting antihistamine 3 days prior to medication reintroduction
   - Cetirizine 10mg or fexofenadine 180mg
   - Consider montelukast 10mg daily

2. Diphenhydramine 25-50mg given 30 minutes prior to TB medication introduction

3. Sequential drug addition every 3-5 days with dose escalation

4. Start with most important drugs
   - Rifampin → INH → PZA → EMB
Med reintroduction example

- Day 1: Rifampin 150mg
- Day 2: Rifampin 300mg
- Day 3 Rifampin 600mg
- Day 4: Rifampin 600mg
- Day 5: Rifampin 600mg, INH 50mg
- Day 6 Rifampin 600mg, INH 100mg
- Day 7 Rifampin 600mg, INH 300mg
- Day 8: Rifampin 600mg, INH 300mg
- Day 9: Rifampin 600mg, INH 300mg, PZA 500mg
- Day 10: Rifampin 600mg, INH 300mg, PZA 1000mg
- Day 11: Rifampin 600mg, INH 300mg, PZA 1500mg
- Day 12: Rifampin 600mg, INH 300mg, PZA 1500mg……
Rash Case 1

- 54 yo male started on INH, RMP, PZA, and EMB. Baseline labs were WNL. After 2 weeks of therapy, he reports a rash on his chest.

- How should we manage?
Rash Case 1

- Confounders: None identified
- Severity assessment: Mild
  - no systemic symptoms, no severe symptoms, mild maculopapular area/itching on center chest
- Treat symptoms: cetirizine 10mg daily, diphenhydratmine 25-50mg 4x daily as needed for itching, topical hydrocortisone 1% 2x daily as needed
- Cease meds: No

Rash resolved within one week, successful completion of 6 months TB therapy
Rash Case 2

• 26 yo female started on INH, RMP, PZA, and EMB. After 2 weeks of therapy, she reports a maculopapular rash on her arms, back, and chest.

• How should we manage?
Rash Case 2

- Confounders: None identified
- Severity assessment: Moderate
  - no systemic symptoms, no severe symptoms, not spreading, decent surface area on her body creating patient anxiety and cosmetic concerns
- Treat symptoms: fexofenadine 180mg daily, diphenhydramine 25-50mg 4x daily as needed for itching, topical hydrocortisone 1% 2x daily as needed
- Cease meds: Yes
- Plan for reintroduction:
  - Await rash resolution, Continue fexofenadine 180mg daily and consider montelukast 10mg daily, provide diphenhydramine 25-50mg 30minutes prior to TB med introduction
Rash resolved within one week, successful completion of 6
Med reintroduction- Case 2

Pt weight 51kg

- Day 1: Rifampin 150mg
- Day 2: Rifampin 300mg
- Day 3 Rifampin 600mg
- Day 4: Rifampin 600mg, INH 100mg
- Day 5 Rifampin 600mg, INH 300mg
- Day 6: Rifampin 600mg, INH 300mg
- Day 7: Rifampin 600mg, INH 300mg, PZA 500mg
- Day 8: Rifampin 600mg, INH 300mg, PZA 1000mg
- Day 9: Rifampin 600mg, INH 300mg, PZA 1000mg

EMB not added back, Susceptible TB isolate (No need to re-introduce)

Patient ceased diphendyramine pre-med after 2 weeks, continued fexofenadine for duration. No further rash.
Rash Case 3

• 21 yo male started on INH, RMP, PZA, and EMB. After 4 weeks of therapy, he reports fever (102 F), malaise, fatigue, reports spreading rash on arms, face, thighs, calves, back, and chest. Notes “the rash is inside my cheeks and my eyelids and itches like crazy”

• How should we manage?
Rash Case 3

• Confounders: None identified

• Severity assessment: Severe
  • systemic symptoms, fever, spreading, large surface area on almost entire body, mucous membrane involvement

• Cease meds: Yes

• Plan: Call 911 if unable to transport patient to ER emergently
Ocular Case 1

• 68 yo male (74kg) started on INH 300mg daily, Rifampin 600mg daily, PZA 1500mg day, and EMB 1200mg daily. Scr 2.6 (CKD). After 4 weeks of therapy, he reports blurry vision and trouble differentiating red/green colors. Uric acid is 12.4mg/dl (3.2 – 6.4mg/dl).

• How would you manage this?
Optic neuropathy

- Toxicity to the optic nerve
- EMB >>> INH / Linezolid
- Thought to be reversible if caught early
- Decrease in sharpness of object appearance (blurred appearance)
- Red/green color blindness can occur
- Greater risk with higher EMB dose/longer duration/renal dysfunction
- EMB must be dose adjusted for renal function
Optic neuropathy management

- Prevention is key
  - Appropriate EMB dose for renal function
  - Vitamin B6 for INH
  - Baseline ophthalmology exam
  - Monthly visual acuity/color discrimination testing (Ishihara)

- If symptoms, hold suspect drugs and send to Ophthalmology emergently
PZA and asymptomatic hyperuricemia

• PZA will increase uric acid level
• More pronounced with higher doses and decreased renal function
• PZA is metabolized by the liver, metabolites are cleared renally
  • Dose adjust for CrCl <30ml/min
• Higher uric acid levels often a marker for medication compliance
Ocular Case 1

- 68 yo male (74kg) started on INH 300mg daily, Rifampin 600mg daily, PZA 1500mg, and EMB 1200mg daily. Scr 2.6 (CKD). After 7 weeks of therapy, he reports blurry vision and trouble differentiating red/green colors. Uric acid is also 11.4mg/dl (3.2 – 6.4mg/dl).

- **Management:**
  - Cease EMB/INH (additional agents added as appropriate)
  - Urgent Ophthalmology referral (i.e. same day)
  - Likely rechallenge with INH after symptom resolution, ensuring vitamin B6 administration
  - No concerns with uric acid, expected, but dose adjust his PZA based on crcl <30ml/min
Pyrazinamide (PZA) – Adv rxns

- Hepatotoxicity / hepatitis
  - modest rises in transaminases; *Slow* hepatic/transaminase recovery is clue to PZA toxicity

- Hyperuricemia
  - can be used as a marker of drug compliancy
  - Development of gout is rare, usually pre-existing

- Arthralgias
  - Non-gouty arthralgia in up to 40% of patients
  - Usually mild and self-limited
  - Doesn’t require treatment discontinuation
  - Usu treat with low dose NSAIDS

- Other: GI upset, rash
Ethambutol – adverse reactions

• **Optic neuropathy** - ↓ visual field; ↓ red-green color discrimination
  - Monitoring - Visual acuity & color vision (baseline and monthly)

• **Contraindications:**
  - Pre-existing optic neuritis (from any cause)
  - Inability (i.e. young pt. age) to report visual disturbances

• **Other:**
  - peripheral neuropathy (rare) - occasionally in legs
  - hair loss (rare)
PN Case

- 53 yo diabetic male started on INH, RMP, PZA, and EMB. After 4 weeks of therapy, he notes feelings of ‘pins and needles’ in his fingers/toes

- What drug is the likely culprit? How can this be prevented?
Peripheral Neuropathy

- Symmetric polyneuropathy
  - Early: paresthesias
  - Late: sensory loss, ↓reflexes, ↓proprioception
- Predisposed in patients with:
  - Alcoholism, diabetes, HIV infection, malnutrition
- TB drugs implicated:
  - Isoniazid, ethionamide, cycloserine, linezolid
- Treatment
  - Start Vit. B6 if not already done so (typically 100-150 mg/d)
  - Stop/change TB drug therapy (if possible)
  - Low dose TCAs or gabapentin (if refractory)
Section 1 Recap

1. Tell ‘em what you’re going to tell ‘em
2. Tell ‘em
3. Then tell ‘em what you told ‘em
Section 1 recap

- Hepatotoxicity management (symptom assessment, degree of transaminitis, graded reintroduction)
- Rash management (Severity assessment, Antihistamine treatment, serial reintroduction)
- Rifampin’s biggest adverse effect is on other meds
- E in EMB means caution for EYES
- PZA increase uric acid
TB med Common AE’s

- INH: peripheral neuropathy, hepatotoxicity,
- RMP: DDI, red/orange body fluids, hepatotoxicity
- PZA: arthralgias, hepatotoxicity, uric acid
- EMB: Ocular toxicity; peripheral neuropathy
Section 2
Adverse Drug Reactions
General Principles - 2nd Line Agents

Less Effective

More Toxic

More Expensive
2nd - line Anti-Tuberculosis Drugs

- Aminoglycosides
  - Streptomycin, Amikacin & Kanamycin
- Capreomycin
- Thioamides
  - Ethionamide
  - Prothionamide
- Fluoroquinolones
  - Moxifloxacin
  - Levofoxacin
  - Ciprofloxacin
- Cycloserine (and Terizidone)
- Para-Aminosalicylic Acid (PAS)
- Other:
  - Linezolid
  - Bedaquiline (TMC 207) – FDA approved 12/2012; a new diarylquiline
  - New nitroimidazoles (investigational)
Case 1

- 44 yo M with MDR TB is on PZA, EMB, Levofloxacin, Amikacin, Ethionamide, and PAS. During the 1st month of therapy patient is really struggling with nausea, dyspepsia, diarrhea, and some mild intermittent vomiting. He doesn’t think he can keep this up.

- How would you manage?
GI effects of TB meds

- Any TB medication can be implicated, more common with 2\textsuperscript{nd} line therapies

- Nausea/Vomitting/Diarrhea:
  -Ethionamide, PAS, Linezolid, FQs, Bedaquiline, Clofazimine

- Significant symptom overlap: Ethionamide and PAS often not tolerated together
Management of GI effects

• Nausea/Vomitting:
  • Rule out hepatotoxicity (LFT assessment)
  • Suspect drug (patient opinion)
  • Hold drug for 3 days to see if improvement
  • Reintroduce tapering dose where appropriate (ETA, PAS, CLZ)
  • Take with light snack/meal
  • Take in evening
  • Premedicate with anti-emetic (ondansetron, metoclopramide, promethazine, lorazepam)
  • Maintain hydration
  • Watch for NSAID use
  • Treat reflux with acid suppressants, address H.Pylori if present
Management of GI effects

• Diarrhea:
  • Rule out other confounding causes of diarrhea
    • Diet change
    • Supplement use
    • Lactose intolerance
  • Rule out other parasitic/infectious causes of diarrhea
    • Cdiff
  • Yogurt/active culture to aid with normal flora
  • Loperamide as needed
  • Maintain hydration
Dose Escalation Strategies: Ethionamide, Cycloserine, PAS

• Ethionamide & Cycloserine
  • Start with 250 mg daily x a few days
  • Increase to 250 mg bid x a few days
  • Increase to 250 mg/qAM and 500 mg q/PM
    • Check serum level

• PAS (Paser granules, sachet packets)
  • Start with 2 gm bid x a few days
  • Increase to 2 gm/qAM and 4 gm qPM x few days
  • Increase to 4 gm bid
    • Check serum level
Case 2

- 44 yo M with MDR TB is on PZA, EMB, Levofloxacin, Amikacin, Ethionamide, and PAS. 3 months into therapy he complains of fatigue, weight gain, and lack of energy. TSH is 8.4 mU/L.

- How would you manage?
Hypothyroidism

- TB drugs implicated:
  - Ethionamide
  - Para-aminosalicylic acid (PAS)
  - Risk increased when both drugs used together (at least 40% incidence; possibly higher)
  - A **reversible** endocrine effect

- Monitoring:
  - Monthly clinical assessments
  - Check TSH baseline and q 3 months
  - Replace with thyroid hormone (levothyroxine) if TSH rises
    - Do not need to stop TB drugs
Ethionamide

- GI intolerance – (high likelihood)
  - N/V, diarrhea; metallic taste/decreased appetite
- Endocrine disorders:
- Peripheral neuropathy (with prolonged therapy) - reversible
- Hepatitis (10% cases) - rarely serious
- Arthralgias
- Caution with co-administration PAS (GI distress, hypothyroidism)
Para-aminosalicylic acid (PAS)

Delayed-release PASER granules (acid-resistant outer coating)

- Bulky, unpleasant taste
- GI disturbance
  - anorexia, nausea, vomiting, abdominal discomfort
- Hypothyroidism, goiter
  - PAS has anti-thyroid effect
- Hepatotoxicity
- Hypersensitivity reaction / skin rash
- Duplicative GI and hypothyroid effects with ethionamide
**Linezolid**

- An oxazolidinone
- 600 mg once daily dosing preferred
  - Twice daily dosing recommended for MRSA and other drug-resistant Gram-positive bacteria

**Select Toxicities include:**
- GI AEs
- Myelosuppression
- Peripheral neuropathy
- Ocular toxicity
- Mitochondrial toxicity; hyperlactatemia
- Serotonin toxicity - when administered in combination with a SSRI or a nonselective MAO inhibitor

Case 3

- 27 yo F (63kg) with MDR TB is on PZA 1500mg daily, EMB 1200mg daily, Levofloxacin 1000mg daily, Amikacin 900mg daily, Linezolid 600mg daily, and cycloserine 500mg twice daily. Patient reports worsening of depression, notable anxiety, difficulty concentrating, has delusions that people are hunting her, and is drawing psychedelic pictures of visions she is having on napkins in the waiting room.

- How would you manage?
CNS Reactions

- **Depression**
  - Cycloserine
  - Ethionamide

- **Psychosis**: Cycloserine, INH (rare)

- **Seizures**: INH, ethionamide

- **Pyridoxine (Vit B6)**
  - Cycloserine, Ethionamide; INH
  - 50 mg Vit. B6 for each 250 mg of cycloserine (variable)
Cycloserine

• CNS toxicity
  – Inability to concentrate and lethargy
  – Seizure, depression, psychosis, and suicidal ideation
    • usually occur at peak concentrations > 35 mcg/ml
    • Can also be seen in the normal therapeutic range
    • Vitamin B6, 100-200 mg/d, to help prevent

• Other Toxicities:
  – peripheral neuropathy
  – Skin problems include lichenoid eruptions and Stevens-Johnson syndrome
Case 3

- Patient has signs of cycloserine toxicity:
  - Worsening psych conditions: anxiety, depression
  - Difficulty concentrating
  - Psychotic features: delusions, images
- Potentially exposure related (high dose)
- Ensure B6 supplementation
- Cease cycloserine
- Consider later tapered reintroduction (lower total dose and confirm level with TDM) based on symptom resolution or an alternative agent for TB
Aminoglycosides/Cyclic Polypeptide

- Audio-toxicity - high frequency hearing loss (irreversible)
- Vestibular dysfunction (irreversible)
- Nephrotoxicity - reversible
- Eosinophilia

**Monitoring:**
- Renal function / Creatinine
- Weekly serum levels
- Baseline audiogram and if hearing changes
Fluoroquinolones

- Moxifloxacin, Levofloxacin more active compared to ciprofloxacin, ofloxacin
- Generally *well tolerated* among 2\(^{nd}\) line TB drugs
- Notable side effects:
  - Tendonitis; tendon rupture (Achilles tendon most common)
  - QTc prolongation
    - Higher risk when given with other QTc prolonging drugs – e.g. bedaquiline, clofazimine, Zofran, azole-antifungals, etc.
  - Insomnia, lightheadedness, dizziness
Bedaquiline

- Increased risk of death (11.4% vs. 2.5% in comparator group)
- Potential for QTc additive effect with other QTc prolonging drugs - caution by FDA
- Hepatotoxicity
- Limited data in HIV co-infected patients
Clofazimine

- Used for MDR TB, Leprosy
- Side effects include:
  - Bronze skin pigmentation (75-100%)
  - GI / stomach upset; N/V (40-50%)
  - QTc prolongation potential
    - Monitor ECG when given with quinolones and/or BDQ
    - Ocular: Conjunctival and corneal pigmentation due to crystal deposits
- Not commercially available
  - Need to submit abbreviated IND to FDA for use
2nd line TB therapy summary

- GI adverse effects can happen with any TB medication, though some are more common (PAS/ETA)
- Administration adjustments, supportive meds, and isolation/dose-escalation/titration can aid with GI effects
- Cycloserine can have psychiatric effects, particularly with higher levels
2nd line TB therapy summary

• 2nd line AEs:
  • Ethionamide: N/V/D, hypothyroidism
  • PAS: N/V/D, hypothyroidism
  • Linezolid: thrombocytopenia, peripheral neuropathy
  • Cycloserine: Worsening psychiatric symptoms, lethargy
  • AGs: kidney toxicity, audiototoxicity, vestibular toxicity
  • FQs: QT prolongation, tendon rupture
  • BDQ: QT prolongation, increased mortality
  • Clofazimine: N/V/D, Skin color changes
Questions?

- TB drug adverse reactions
- Management of toxicity