TB Drugs Side Effects and Toxicity (or)

David E. Griffith MD
Professor of Medicine
National Jewish Health
Denver, CO

Or, Drugs that make you….

Vomit, Barf, Blow chunks, Bow down before the porcelain god, Chuck your Cheerios, Cough up your cookies, Emesis, Empty your stomach, Flash, Heave, Hurl, Jersey yodel, Lose your lunch, Puke, Regurgitate, Retch, Spew, Spit up, Throw up, Tonsil toss, Toss your cookies, Up-chuck, Urp, Ralph, Calling dinosaurs, Technicolor yawn, Chunder, Talk on the big white telephone, Boot, Drive the porcelain truck

Disclosures

- Insmed Inc.: Grant recipient, consultant, speaker
- AN2 Therapeutics: Consultant
- Paratek Pharmaceuticals: Consultant

No Disclosures related to this talk

Objectives

After attending this lecture, participants should be able to describe:

- Side effects of common TB drugs
- How to avoid TB drug side effects
- How to monitor for TB drug side effects
- How to manage side TB drug side effects

Outline

- A discussion of the 1st line TB drug side effects with an emphasis in INH hepatotoxicity
- Strategies for monitoring patients for TB drug side effects
- A discussion of more commonly used 2nd line TB drug side effects
- The impact of side effects on TB drug regimens

INH Toxicity

- **Transaminitis**
- **Peripheral neuropathy**
- Central Nervous System Effects: irritability, seizures, dysphoria, inability to concentrate
- Lupus-like syndrome: 20% develop antinuclear antibodies (1), < 1% develop clinical lupus erythematosus
- Hypersensitivity Reactions: fever, rash
- GI reactions (nausea, anorexia, abdominal pain)
- Drug Interactions: levodopa, phenytoin, valproic acid, carbamazepine

(1) Ann Intern Med. 1978 May;88(5):650-2.

INH Hepatotoxicity

- Mechanisms: unknown
- Asymptomatic elevation of aminotransferases: 20% of patients
- Clinical hepatitis: 0.6% of patients
- Fulminant hepatitis (hepatic failure): Approximately 4/100,000 persons completing therapy
- Generally occurs after weeks to months (rather than days to weeks)
- Risk factors: Age, alcohol consumption (> 4X î risk w/daily ETOH), pregnant and post-partum women, active hepatitis B, other hepatotoxic drugs

Am J Respir Crit Care Med. 2006 Oct 15;174(8):935-52

Isoniazid Hepatotoxicity: Interventions (AJRCCM, 2006; 174: 935-952)

- “Isoniazid should be withheld if ALT is at least three times the ULN when jaundice and/or hepatitis symptoms are reported, or if ALT is at least five times the ULN in the absence of symptoms”
- “A rapid increase in ALT may be an indication for more frequent monitoring…”
- Consider rechallenge (many caveats)

INH Peripheral Neurotoxicity

- Dose Related, Functional vitamin B6 deficiency (blocking conversion of B6 to pyridoxal phosphate/enhance excretion (1))
- Uncommon (< 0.2%) at conventional doses
  - Increased risk for neuropathy: Diabetic, alcoholic, HIV infection, pregnancy, poor nutrition, hypothyroidism
- Retrobulbar (optic) neuritis: reported.
- Pyridoxine recommended to be given to all patients with risks (2)

Administer Vitamin B6 (pyridoxine) 50mg daily. 100mg daily with neuropathy (2)

Note: B6 in doses greater than 200mg can CAUSE neuropathy

1) Kucers' The Use of Antibiotics 7th p2330, 2)IDSA Guideline 2016

INH Drug Interactions

- Increased concentrations of:
  - Anticonvulsants
    - Phenytoin, Barbiturates
    - Warfarin
- Decreases concentrations
  - Azole antifungals
- Inhibits histaminase and monoamine oxidase
- INH absorption inhibited by aluminum
  - Avoid antacids containing aluminum

INH Toxicity Monitoring

- The critical element for INH toxicity monitoring is CLINICAL MONITORING.
- Clinical monitoring of patients on INH is absolutely necessary to do, absolutely necessary to do well and absolutely necessary to document well.

Fulminant Hepatic Failure with INH
A few (sobering) thoughts

- Can occur at any time during course of INH treatment
- Can occur in children
- Can occur within a few days of symptom onset even with prompt discontinuation of INH

RIF Toxicity

- **Well tolerated medication: Only 1.9% had to switch LTBI therapy.**
- **Orange discoloration of body fluids**
- **Drug interactions** due to induction of hepatic microsomal enzymes (CYP 450)
- Cutaneous Reactions: 6%, generally self- limited
- Pruritus/flushing (usually 2-3 hours after the dose)
- Gastrointestinal symptoms: nausea, anorexia, abdominal pain
- Hepatotoxicity: nearly 0% as monotherapy, 2-3% with INH, **cholestatic**
- Hematological: Leukopenia, thrombocytopenia

Rifamycin Metabolism (Rifampin, Rifabutin, Rifapentine)

- Rifampin and rifabutin are both cleared by the liver >> kidneys
- Rifampin and rifabutin are both inducers of the CYP3A4 in the cytochrome P450 enzymes and transporters
  - Rifampin causes and 80-fold induction and rifabutin causes a 20-fold induction in human hepatocytes
  - Common medications to consider in drug-drug interactions prednisone, HIV medications, warfarin, beta blockers, azoles, birth control medications, hormone replacement medications, thyroid replacement, statins, etc.

Rifamycin Toxicity

- Hematologic
- Hepatotoxicity
- Nephrotoxicity
- Hypersensitivity
- “Lupus syndrome”
  - Fever, Rash, Leukopenia, thrombocytopenia, arthralgias
- Nausea and vomiting

Photos used with patient permission

RIF Toxicity

- Flulike symptoms: < 1% of patients on intermittent therapy.
  - usually appears after 3 – 6 months of Int. dosing. (0.4-0.7%)
- Severe immunologic reactions: thrombocytopenia, hemolytic anemia, acute renal failure (AIN/ATN) and thrombotic thrombocytopenic purpura (each < 0.1% of patients)
- Paroxysmal, serendipitous, idiosyncratic
  - Cannot be predicted

Rifabutin

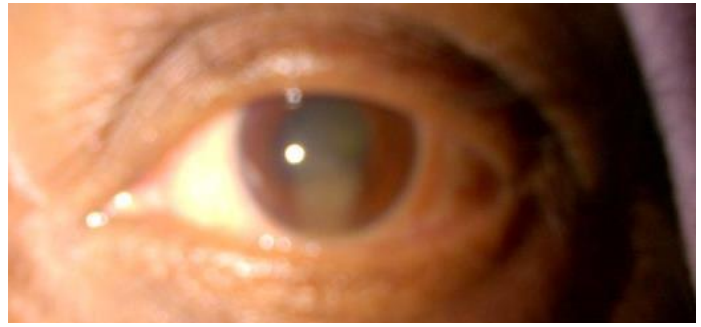
- A substitute for rifampin for patients who are receiving drugs, especially antiretroviral drugs, that have unacceptable interactions with rifampin.
- Adverse effects: Less severe induction of hepatic microsomal enzymes, therefore, less effect on the metabolism of other drugs

- Adult dose 5 mg/kg (300 mg daily, 2-3X/week).

(1) IDSA 2016 guideline

Rifabutin Toxicity

- Hematologic toxicity: neutropenia and thrombocytopenia
- Drug interactions: less severe than rifampin
- Uveitis: Rare, < 0.01% (Combination with macrolides)
- GI Symptoms
- Polyarthralgia: 1-2% at standard doses
- Pseudojaundice (HIV, with clarithromycin and EMB)
- Hepatotoxicity, flu-like syndrome



Rifapentine Pharmacology

Egelund EF and Peloquin CA Expert Rev Clin Pharmacol. 2016 Aug [Epub ahead of print]
Alfarisi O et al. Expert Rev Clin Pharmacol.2017;10:1027

- Due to the shared mechanism of action between the rifamycins, cross-resistance occurs
- A similar spectrum of activity to rifampin
  - MIC against MTB is two to fourfold lower than rifampin's, ranging from 0.01 to 0.06 µg/mL
- Food significantly impacts rifapentine's bioavailability,
  - meals can increase rifapentine's exposure from 33% to 86%, depending on meal composition, with high-fat meals having the greatest impact on bioavailability.
- Rifapentine's increase in bioavailability when administered with food is the opposite of rifampin's, which decreases with food administration.

Rifamycins – Rifampin, Rifabutin, Rifapentine

Problems

- GI distress, reflux, flatulence, diarrhea

- Flu-like symptoms
- Rash, uveitis, joint pain
- Hepatitis
- Cytopenias (WBC, platelet)
- Anaphylaxis / severe allergic reaction

Guidance

- Administer with food, probiotics, acid suppression*, anti-nauseas drugs[+], loperamide[+]
- May require discontinuation
- May require discontinuation
- Stop/restart medication at lower dose
- Monitor CBC; may need to discontinue
- Immediate discontinuation and treat allergic reaction. May consider desensitization with help of Allergy Consultation

*acid suppression reduces rifamycin absorption; [+]May prolong QTc

Drug Interactions

Rifampin

- Interactions due to induction of hepatic microsomal enzymes (cytochrome P-450, CYP, enzyme system) that accelerate metabolism of multiple drugs
- Major concern is reduction in serum concentrations of common drugs to ineffective levels
- Bidirectional interactions between rifamycins and antiretroviral agents
- Bidirectional interactions with INH

Common Rifampin Drug Interactions

IMPOSSIBLE TO REMEMBER ALL

Remember potential life threatening int.

- Oral anticoagulants
- Digoxin/Amiodarone/Anti-arrhythmics
- Methadone/Phenytoin
- Cyclosporine/Tacrolimus
- Itraconazole/ketoconazole
- **Antiretrovirals**
- **Oral contraceptives**

- **Co-operation of patient's PCP required**

Useful Websites

- Lexicomp®
- https://www.wolterskluwercdi.com/

HIV meds

- Liverpool HIV Interaction checker
- https://www.hiv-druginteractions.org/
- UCSF website
- http://hivinsite.ucsf.edu/interactions

EMB Toxicity

- **Retrobulbar neuritis**: decreased visual acuity or red-green color discrimination, dose related, unusual at dose 15 mg/kg. Increased risk with renal insufficiency.
- Peripheral neuritis
- Cutaneous reactions: < 1% of patients

EMB Ocular Toxicity

- Can be one or both eyes.
- **Axial (central)** vs. periaxial (peripheral) retrobulbar neuritis
- Mechanism: Autophagy dysregulation (?)
- Central nerves with optic nerve are commonly affected, and may cause blurry vision, central scotomas, and loss of the color discrimination.
- Fundoscopic exam is usually normal.

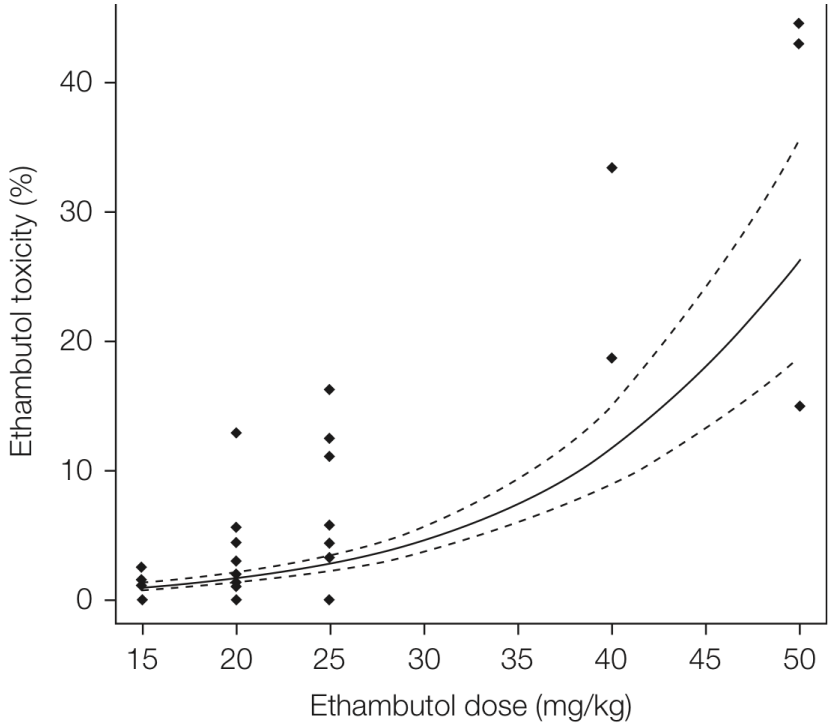


Figure 124.2. Ocular toxicity and dose of ethambutol. $y = \exp(-6.0599 + 0.l006*\text{dose})/(l + \exp(-6.0599 + 0.l006*\text{dose}))$. The broken lines represent the 95% confidence interval limits. (From WHO, 2006.)

Kucers' The Use of Antibiotics 7th

Ethambutol Optic Neuropathy

- Usually reversible but may take several months (steroid not indicated)
- Risk increases with dose(>20mg/kg) AND decreased renal function
- TIW dosing with renal insufficiency
- Give after hemodialysis

Griffith DE, Am J Respir Crit Care Med 2005 Jul 15; 172:2

EMB Toxicity: Monitoring

- All patients should have baseline visual acuity (**Snellen chart**) and testing of color vision discrimination (**Ishihara tests**).
- PATIENT EDUCATION
- Monthly symptom check (blurred vision scotoma)
- Monthly testing: high doses, treatment longer than 2 months, renal insufficiency
- Ophthalmology evaluation, no single diagnostic test for ethambutol ocular toxicity

EMB Ocular Toxicity

- Management
- Discontinue EMB immediately
- Refer to ophthalmology ASAP
- If severe, consider discontinuing EMB, INH, linezolid
- Recovers over weeks to months, but defective color vision may persist longer.

Pyrazinamide (PZA) Toxicity

- **Hepatotoxicity**: Less at 25 mg/kg than 50 mg/kg
- **Gastrointestinal symptoms**: nausea and vomiting mild at standard doses.
- Non-gouty polyarthralgia: Up to 40% of patients: not an indication to stop therapy.
- **Asymptomatic hyperuricemia**: Expected (blocking excretion)
- Acute gouty arthritis: Unusual except in patients with pre-existing gout.
- Rash/dermatitis: usually self limited

Kucers' The Use of Antibiotics 7th

Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active TB

	Dose (mg/kg)	Rash	Hepatitis	GI
INH	(5.2)	4	5	4
RIFAMPIN	(10.2)	9	0	4
PZA	(24.2)	8	7	3
EMB	(16.8)	0	0	0

Am J Respir Crit Care Med. 2003 Jun 1;167(11):

Fluoroquinolones - Moxi, levo or ciprofloxacin

- Though usually well tolerated, side effects are common
  - GI distress – probiotics, saltine crackers, acid suppression, timing
  - Musculoskeletal pain – if moderate/severe may require discontinuation
  - Neurologic – anxiety/tremulousness are common. Avoid caffeine if possible
- Less common or rare but important
  - Tendinopathy – cessation of drug
  - QTc prolongation – baseline and periodic EKG (don't forget to review the medication list to look for other drugs that prolong QT)
  - Psychiatric manifestations (genetic ?)
  - Clostridioides difficile diarrhea
  - Avoid in patients with myasthenia gravis, may precipitate myasthenic crisis

Fluoroquinolone Heptotoxicity

- Moxifloxacin metabolized in part by the liver, levofloxacin excreted unchanged by the kidneys: no dosage adjustment necessary in renal insufficiency.
- Reversible transaminase elevation among the fluoroquinolones in 2 to 3% of cases
- Moxifloxacin: transaminase elevation >1.5 times ULN in 0.9% of cases
- Levofloxacin: severe hepatotoxicity-RARE

Fluoroquinolone Toxicity
Musculoskeletal

- Tendonitis/Tendon Rupture (*Black box* warning)
- If tendon inflammation is mild:
  - Rest the joint/NSAID's
  - Reduce dose of FQ if possible
  - If symptoms progress, stop the FQ
- If tendon inflammation is moderate/severe
  - Stop the FQ
  - Rest the joint/NSAID's
  - Risk/benefit evaluation of FQ continuation
- Tendon rupture (usually Achilles) is rare

Quinolone Pearls

- Things to watch for with moxifloxacin
  - Best on empty stomach
  - Don't take within 2 hours of calcium/magnesium/iron containing supplements or foods
  - Take in AM because of caffeine-like effects
  - Use with caution in the elderly because of CNS side effects, hypoglycemia, and tendonitis

Clofazimine For Mycobacterial Disease

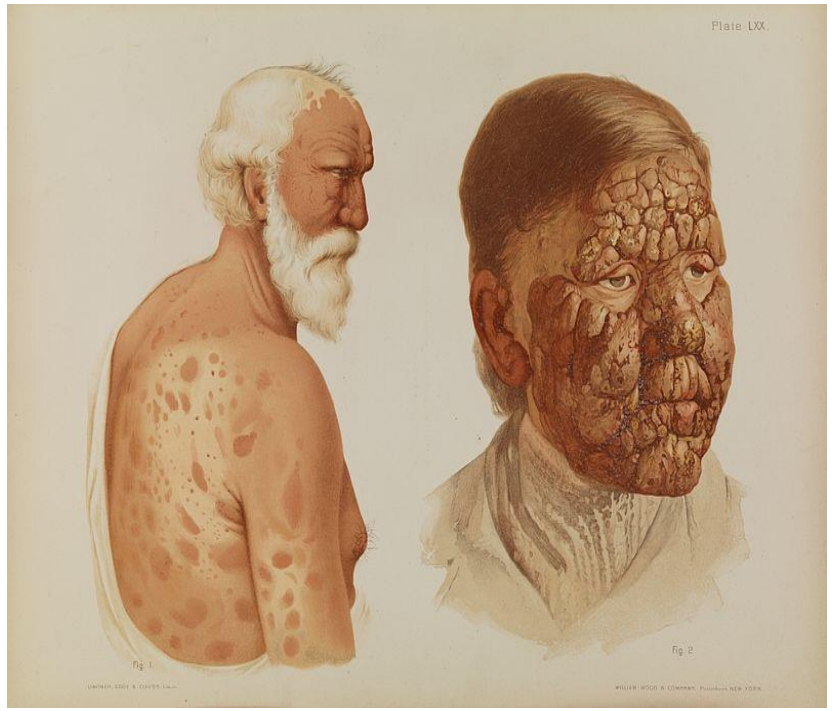
Clofazimine – originally developed as a drug for Hansen's Disease. Novartis introcuced it in 1969, "Lamprene".

Exact mechanism is unknown –inhibits mycobacterial DNA replication and cell growth.

Optimal dosing not established

Cross resistance with bedaquiline

Only available in the United States under IND from the FDA/obtain drug from Novartis



Clofazimine for Mycobacterial Disease: Adverse effects

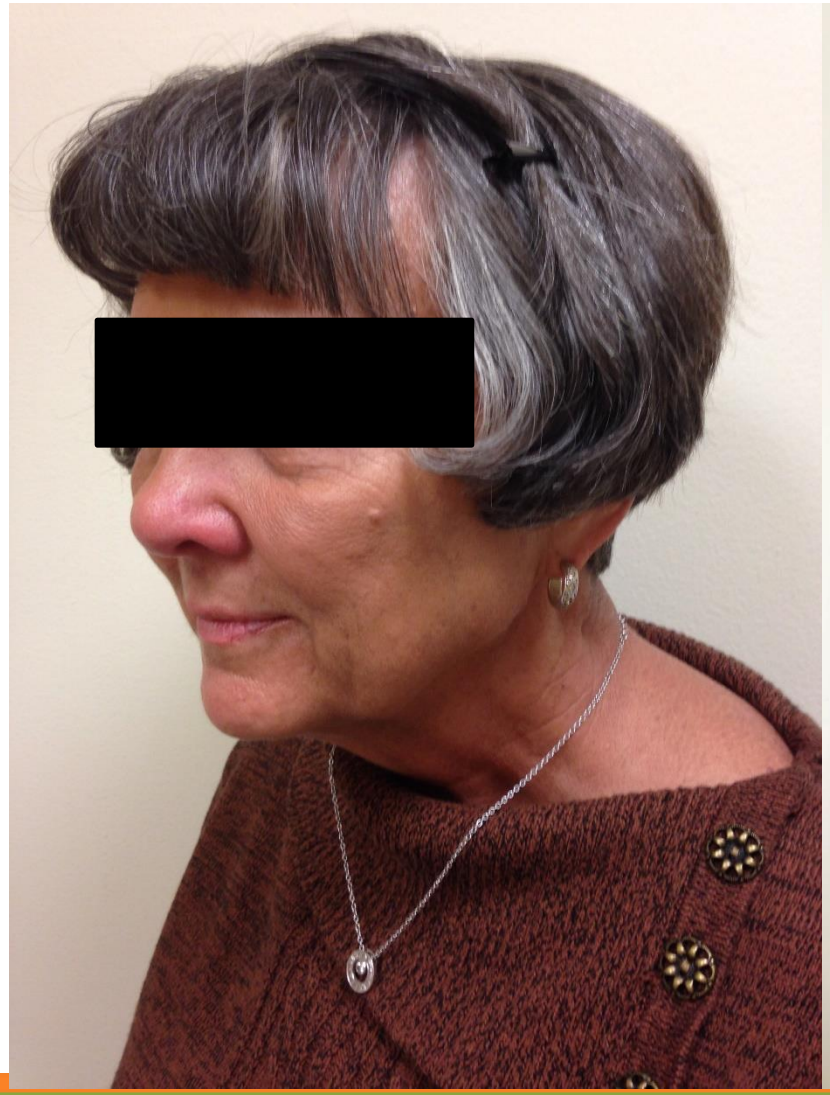
Common

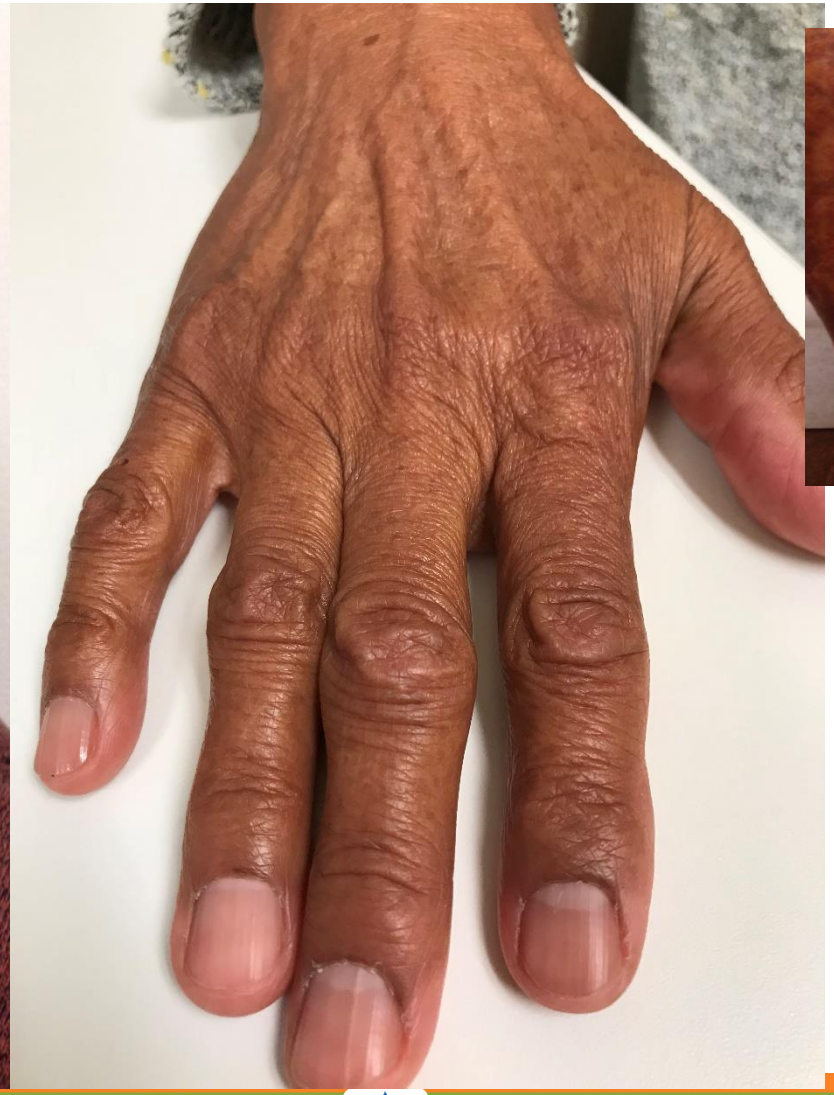
- QTc
- Diarrhea
- Skin discoloration
- loss of appetite
- nausea or vomiting
- skin rash and itching

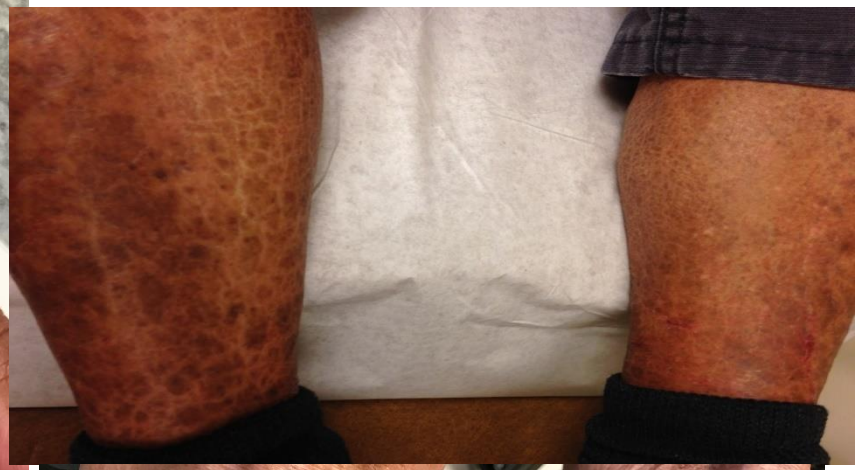
Less common or rare

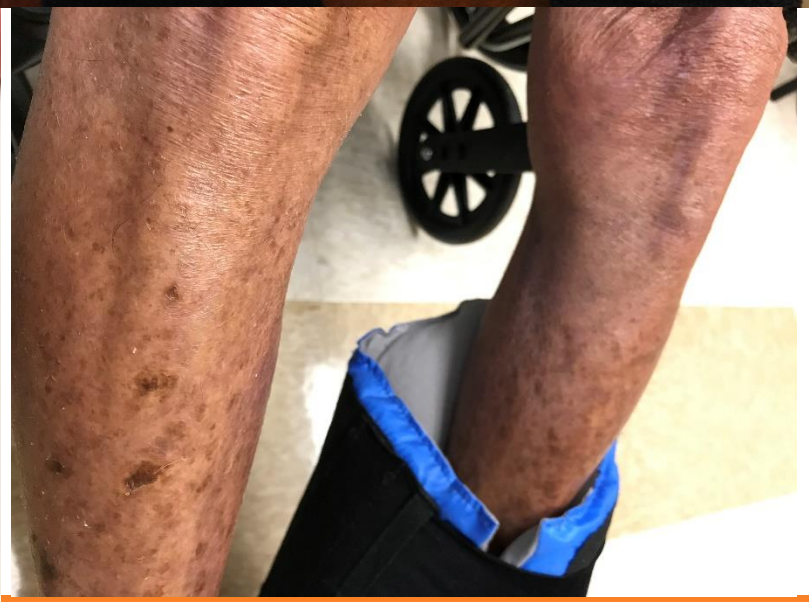
- Changes in taste
- dryness, burning, itching, or irritation of the eyes
- increased sensitivity of skin to sunlight
- Bloody or black, tarry stools
- colicky or burning abdominal or stomach pain
- mental depression

What about clofazimine?:









Bedaquiline and Mycobacterial Disease

- There are concerns about QTc interval prolongation, unexplained association with death and potential for hepatotoxicity. Initial concerns about sudden death with bedaquiline NOT confirmed
- Good treatment responses and safety profiles have been substantiated by several studies
- Dose adjustment is not required in case of mild-to-moderate renal impairment

Bedaquiline For Mycobacterial Disease

Side effects:

- Nausea
- QTc prolongation
- Headache
- Chest pain
- Weight loss
- Rash/skin discoloration
- Increase in LFTS/amylase

Linezolid for Treatment of Tuberculosis

-Very active in vitro against drug susceptible and drug resistant MTB Can be given orally

- Optimal dose unknown: Adverse events dose related

-Frequent, severe adverse events:

bone marrow suppression- dose dependent/ reversible

peripheral Neuropathy- Not dose dependent (? not reversible)

Optic neuritis

-Dosing from 600 mg TIW to 600 mg/day

Linezolid for Treatment of Tuberculosis

GI disturbance

Rash

Serotonin syndrome? Most cases have been associated with the concomitant use of LZD and an SSRI or tricyclic antidepressant.

Linezolid-associated serotonin toxicity even with concomitant use of serotonergic agent “exceedingly rare”

Kufel WD et al Int J Antimicrobial Agents 2023, 62; 106843. **0.11% 1743 patients**

Pretomanid for Mycobacterial Disease

- Pretomanid is a nitroimidazole that shares the same mechanism of action with delamanid,
- Bactericidal against actively replicating mycobacteria (inhibiting mycolic acid biosynthesis) and non-replicating mycobacteria (generating nitric oxide inside the tubercle bacilli)

Pretomanid for use in Mycobacterial Disease

- Owing to similar structure, pretomanid shares cross-resistance with delamanid as well as a relatively high propensity to acquiring bacillary drug resistance
- FDA approved (Limited Population Pathway for Antibacterial and Antifungal Drugs) for clinical practice use in the U.S.

Pretomanid

- fast or pounding heartbeats, fluttering in your chest, shortness of breath, and sudden dizziness (like you might pass out);
- tremors, weakness, problems with balance;
- vision changes;
- severe ongoing nausea and vomiting;
- cough with mucus or blood;
- shortness of breath, chest pain that gets worse when you breathe or cough;
- nerve problems--numbness, tingling, burning, or prickly feeling in your arms, hands, legs, or feet;
- liver problems--nausea, loss of appetite, stomach pain (upper right side), tiredness, itching, dark urine, jaundice (yellowing of the skin or eyes); or
- low blood cell counts--fever, easy bruising, unusual bleeding, pale skin, cold hands and feet, feeling light-headed.

Pretomanid

- nerve problems;
- heartburn, stomach pain, loss of appetite, nausea, vomiting, diarrhea;
- cough, chest pain;
- headache, muscle and bone pain;
- acne, rash, itching;
- abnormal blood tests that check the function of your liver or pancreas;
- unusual weight loss; or
- low blood sugar--headache, hunger, sweating, irritability, dizziness, fast heart rate, and feeling anxious or shaky.

Hepatotoxicity of TB Drugs
Drug Induced Liver Injury (DILI)

- **Hepatotoxic**
  - **INH**
  - **Rifampin/Rifabutin**
  - **PZA**
  - Ethionamide
  - PAS
  - (Fluoroquinolones)
  - Pretomanid/PZA combination
- Non-hepatotoxic (“Liver friendly”)
  - **Ethambutol**
  - Cycloserine
  - Strep/Amikacin
  - Capreomycin
  - (Fluoroquinolones)
  - Someone hand me my 10 foot pole

Risk Factors for Hepatotoxicity

- Alcohol use
- Chronic viral hepatitis
- Older age (> 35 years?)
- Pregnancy or within 3 months postpartum
- Concomitant hepatotoxic meds
- Baseline abnormalities

<u>Monitoring Hepatotoxicity</u>

- Routine laboratory monitoring is not recommended if no risk factors.
- Repeat ALT (CMP) in 2 – 4 weeks if risk factors or GI symptoms.
- Bil/INR/APTT
- Anyone and Everyone?

Management*

- Hold medication if
  1. ALT > 3 times w/ symptoms

     OR

  2. ALT > 5 times w/o symptoms

Immediate switch to liver "friendly" meds depends on the clinical situation.

- Transaminitis is not always due to Tb meds.
  - Consider alternative cause
  - Hepatitis, Alcohol, Acetaminophen
  - Disseminated Mtb
  - NASH

*Validated for INH only

Am J Respir Crit Care Med. 2006 Oct 15;174(8)

Interventions for Hepatotoxicity (PZA sparing: Common Scenario)

- After ALT **<2X ULN**: restart RMP ± EMB
- After 3-7 days: restart INH

- If symptoms recur: stop the last drug added
- If RMP and INH tolerated: do not restart PZA

- Advantage: 2 most potent TB drugs
- Disadvantages: 9 month regimen, still potentially hepatotoxic

Am J Respir Crit Care Med. 2006 Oct 15;174(8)

Rash

- All Mtb meds can cause rash.
- Consider other causes
  - Other medications, new soaps/detergents
  - Insect bites (bed bugs), Xerosis, Herpes Zoster and Scabies

- **Minor rash or itching**
  - Flushing: PZA or RIF
  - Manage symptomatically with antihistamines or topical steroid
  - Continue meds
- **Petechiae**
  - Check thrombocytopenia, such as RIF
- **Generalized rash**
  - Suggestive of a hypersensitivity, check if any mucosal involvement
  - Stop all meds until symptoms resolve, and rechallenge one by one

QT interval prolongation

- Flouroquinolones
  - Moxifloxacin>levofloxacin>ofloxacin>ciprofloxacin
- Bedaquiline (diarylquinoline)
- Clofazimine
- Risk of torsades de pointes unknown
- Optimal screening and monitoring unknown
- Classic example of risk/benefit assessment

Questions?

TB Disease: Baseline Testing and Monitoring

Activity	Baseline	Month of Treatment Completed 1	2	3	4	5	6	7	8	End of Treatment Visit
MICROBIOLOGY										
Sputum smears and culture[1]	☐	☐	☐	☐	☐					☐
Drug susceptibility testing[2]	☐			☐						
IMAGING										
Chest radiograph or other imaging[3]	☐		☐							☐
CLINICAL ASSESSMENT										
Weight[4]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Symptom and adherence review[5]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Vision assessment[6]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
LABORATORY TESTING										
AST, ALT, bilirubin, alkaline phosphate[7]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Platelet count[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Creatinine[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
HIV[9]	☐									
Hepatitis B and C screen[10]	☐									
Diabetes Screen[11]	☐									

IDSA guideline 2016