TB Drugs Side Effects and Toxicity (or)

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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 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



Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229

- CDC project to monitor SAEs with treatment of LTBI 2004-2008
- 17 patients with SAEs, all hepatotoxicity
  - 2 children < 15 yrs of age
  - Adults median age 39
  - Diagnosed between 2nd and 9th month
  - One patient HIV seropositive for Hep C, HIV
  - 5/17 liver transplant (one child), 5/17 died (one transplant)

Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229

- 10 patients with CDC on-site investigation
- All patients had indications for LTBI treatment, were prescribed INH within recommended dosage range, took the medication as prescribed
- Prescribers followed ATS/CDC guidelines for monthly clinical monitoring
- Baseline ALT WNL for 5 patients, 2 patients with monthly ALT monitoring

Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229

- 10 patients with CDC on-site investigation
- Symptoms 1-7 months after INH started
- Fatigue, nausea, abdominal pain in 7 patients who waited for jaundice to seek medical attention
- 3/10 with possible predispositions
- 7/10 patients diagnosed by provider other than the prescriber of INH
- 2 patients INH discontinued within 3 days of symptoms, 8 stopped at least one week after symptom onset, all after medical instruction

Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229

- Death and liver transplantation approximately 1/150,000-1/220,000 patients receiving LTBI treatment
- All patients monitored according to current guidelines
- SAEs idiosyncratic reaction, independent of dosing, possible anytime during treatment, can occur in children

Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229

- "Medical providers should emphasize to patients that INH treatment should be stopped immediately upon the earliest onset of symptoms (e.g. excess fatigue, nausea, vomiting, abdominal pain, or jaundice), even before a clinical evaluation has been conducted, and that initial symptoms might be subtle and might not include jaundice."

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.

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

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

RIF Toxicity

- **Well tolerated medication: Only 1.9% had to switch.**
- **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
- “Influenza syndrome”
- “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)

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

Common Rifampin Drug Interactions

IMPOSSIBLE TO REMEMBER ALL

Remember potential life threatening int.

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

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.

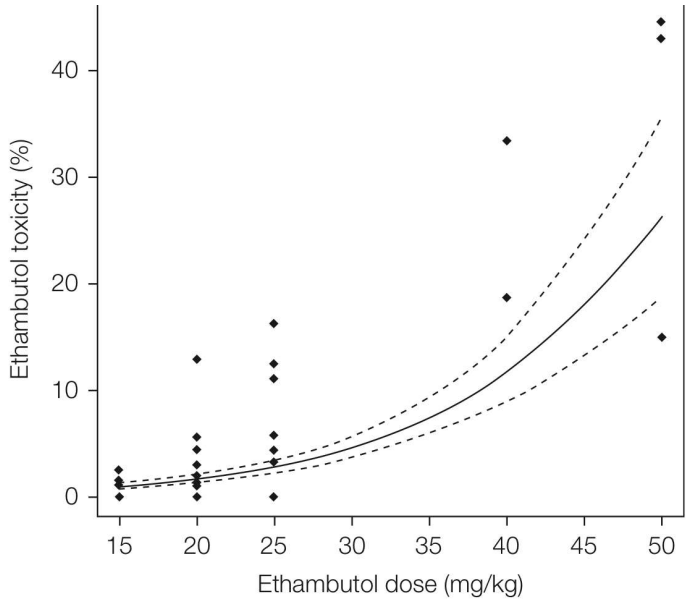


Figure 124.2. Ocular toxicity and dose of ethambutol. $y = \exp(-6.0599 + 0.l006*\text{dose})/(l + \exp(-6.0599 + 0.l006*\text{dose}))$. The broken lines represent the 95% confidence interval limits. (From WHO, 2006.)

Kucers' The Use of Antibiotics 7th

Ethambutol Optic Neuropathy

- May be unilateral or bilateral
  - Decreased visual acuity (blurriness), scotoma (partial vision loss/blind spots), and/or color blindness
- Usually reversible but may take several months(prednisone not indicated)
- Risk increases with dose(>20mg/kg) AND decreased renal function
- Monitor special groups and educate your patients
  - Recommend daily vision self-checks
  - Patients should promptly report to TB clinic personnel new vision changes and to stop the ethambutol immediately until they can be seen by ophthalmology

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
- If severe, consider discontinuing EMB & INH
- Recovers over weeks to months, but defective color vision may persist longer.
- Refer to ophthalmology

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 ?, concomitant cycloserine)
  - 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

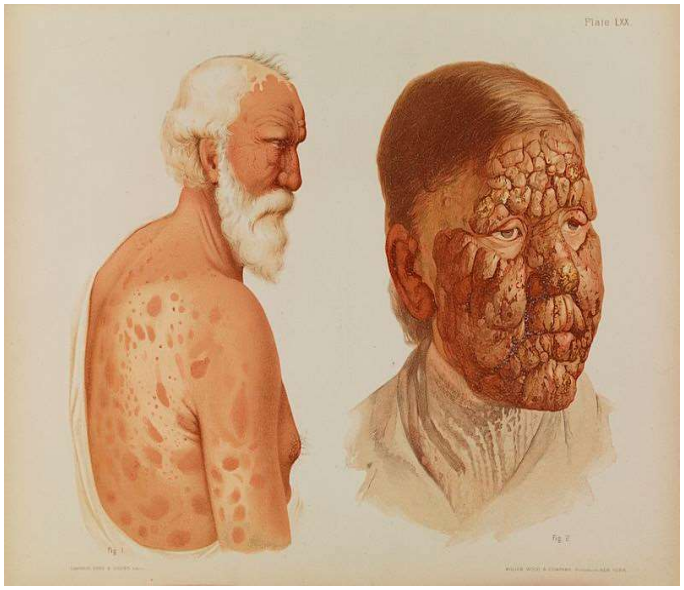
Clofazimine For Mycobacterial Disease

Clofazimine – originally developed as a drug for Hansen's Disease. Novartis launched the product in 1969 under the brand name Lamprene.

Exact mechanism is unknown - binds preferentially to mycobacterial DNA, thereby inhibiting DNA replication and cell growth.

Cross resistance with bedaquiline

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



Clofazimine for Mycobacterial Disease

Side Effects

Common

- 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?:









Clofazimine

- Concerns about protracted reddish-brown skin discoloration and possible stigmatization, alongside potential for developing cross-resistance with bedaquiline and adversely prolonging the QT interval through interaction with other QT-prolonging drugs, may hamper use of clofazimine

HEARTLAND
NATIONAL TB CENTER
A PARTNERSHIP OF UT HEALTH NORTHEAST AND TCID

BPaL is YOUR PaL

Bedaquiline, Pretomanid, Linezolid

Drug susceptible TB, rifampin resistant TB, MDR-TB, XDR-TB

Good for what ails ya

Bedaquiline and Mycobacterial Disease

- There are concerns about QT 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
- QT 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.

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)

- 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

Monitoring Hepatotoxicity

- 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

Treatment in Renal Failure

- **INH** - Decrease dose if severe, monitor drug concentrations
- **Rifampin -** No dose adjustment
- **Ethambutol -** Reduce dose or increase intervals
- **Pyrazinamide -** Use with caution
- **Pretomanid** – No adjustment with mild/moderate renal impairment, “caution” for ESRD/dialysis patients
- **Bedaquiline -** No adjustment with mile/moderate renal impairment, “caution” for ESRD/dialysis patients
- **Linezolid** - No dose adjustment (accumulation of drug and metabolites, TDM)

Treatment in Pregnancy

- **INH** - Safe, give with pyridoxine
- **Rifampin** - Manufacturers caution, may be used safely
- **Ethambutol** - Safe
- **Pyrazinamide -** Little known
- **Fluoroquinolones** - Avoid may cause fetal joint abnormalities
- **Linezolid** - Risk/Benefit (limited data), Breast milk concentration similar to Mom
- **Bedaquiline** – Safe
- **Pretonamid –** Not approved for pregnancy or children

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

Aminoglycosides

Side Effects/Toxicity		Management
• Nephrotoxicity	→	• Electrolyte panel
• Ototoxicity	→	• Audiogram
• Vestibular toxicity	→	• Vestibular testing
• Electrolyte abnormality	→	• Replacement therapy
• Eosinophilia	→	• Not significant
• Local soreness	→	• Ultrasound, hot packs, lidocaine

Parenterally Administered Drugs

- Streptomycin
  - Ototoxicity: vestibular and hearing disturbances, risk increased with age, lasix, dose and cumulative dose
  - Neurotoxicity: perioral parasthesias
  - Nephrotoxicity: 2% of patients, less common than with amikacin or capreomycin

Amikacin

- Amikacin
  - Ototoxicity: hearing disturbances, less vestibular dysfunction than Strep
  - Nephrotoxicity: 3.4-8.7% of patients, increased risk with pre-existing renal disease, higher doses, other nephrotoxic drugs
  - Rash
  - Electrolyte disturbances: hypoklemia, hypomagnasemia (cardiac dysrhythmias)

Capreomycin

- Capreomycin
  - Ototoxicity
  - Nephrotoxicity
  - Electrolyte disturbances: hypoklemia, hypomagnasemia, cardiac dysrhythmias
  - Rash

Aminoglycosides, capreomycin

- Baseline and monthly serum creatinine and Calculated creatinine clearance
- Lower initial dose in patients over age 59 yrs. (10 mg. per kg.; max. dose 750 mg.)
- If baseline creatinine clearance less than 70ml./min., consider use of intermittent dosing initially
- Monitor peak and trough serum drug levels and adjust dose accordingly
- Baseline audiogram, vestibular testing, Romberg testing
- Repeat audiogram or vestibular testing if symptoms develop

Where is the baby?
Did anyone check the bathwater?

- **“Regimens to treat MDR-TB: past, present and future perspectives” (Pontali et al 2019, ERJ; 28: epub)**
- “The negative effect of the injectables on outcomes could be due to the decision by the treating clinicians to use them in the worst clinical cases, based on the resistance profile or despite it. Another possible bias could be due to changing drugs during the course of treatment or misclassification of treatment outcomes. Therefore, rather than concluding that the injectable should avoided, the study emphasized the relevance of the use of… fluoroquinolones , bedaquiline, linezolid and clofacimne.”

Cycloserine

"Psychoserine"

- Cycloserine
  - Central Nervous System Effects: headaches, restlessness, suicidal ideation psychosis, seizures (3% 500 mg/day). May exacerbate underlying seizure disorders or mental illness. Pyridoxine at 100-200 mg/day may help prevent neurotoxic side-effect.
  - Administer with caution to alcoholics, patients with hx of mental illness or seizures
  - Peripheral neuropathy
  - Rash

Cycloserine

- Cylcoserine
  - Dosing can be split if necessary
  - Single dosing facilitates drug level determinations
  - Drug levels are necessary
    - (peak levels 20-35 mcg/ml)

Ethionamide

- Ethionamide
  - Gastrointestinal Effects: “commonly causes profound GI side-effects”. Symptoms may improve if taken with food or at bedtime
  - Hepatotoxicity: 2% of patients
  - Neurotoxicity: Peripheral neuritis, optic neuritis, depression, psychosis
  - Endocrine Effects: blood glucose abnormalities hypothyroidism, gynecomastia, hair loss

P-Aminosalicylic acid (PAS)

- P-Aminosalicylic acid (PAS)
  - Gastrointestinal Distress: 11% of patients, less with lower doses
  - Hepatotoxicity: 0.3% of patients (including jaundice)
  - Malabsorption syndrome
  - Hypothyroidism: common with prolonged administration or concommitant ethionamide
  - Rash, lymphadenopathy, leukocytosis, arthralgia

Questions?