Adverse Drug Reaction in TB

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Anti-tuberculosis Drugs

- First-Line drugs
  - Isoniazid
  - Rifampin
  - Rifapentine
  - Rifabutin*
  - Ethambutol
  - Pyrazinamide

*Not FDA approved for TB

- Second-Line Drugs
  - Cycloserine
  - Ethionamide
  - Levofloxacin*
  - Moxifloxacin*
  - PAS
  - Streptomycin
  - Amikacin/Kanamycin
  - Capreomycin
  - Linezolid
  - Bedaquiline
  - Pretomanid
  - Delamanid*

IDSA Guideline 2016

Why Do We Need Four Drugs?

- Mtb produces drug-resistant mutants during replication, which are generally specific for a single agent.
  - Spontaneous single INH/RIF resistant mutants: $1/10^6$ & $1/10^8$
  - Spontaneous double INH/RIF resistant: $1/10^{14}$
- Multidrug TB treatment provides cross-coverage against these various mutations.

  Pansusceptible Mtb => Can discontinue Ethambutol (2)

- Different Action of Mtb Drugs

Clinical Tuberculosis 5th Edition 2014

Terminology for Mtb PK/PD

- Bacteriostatic vs. Bactericidal
  - Early bactericidal activity (EBA)
- Sterilizing activity – Kill off the “persisters”/Semi-dormant
- Prevention of Emergence

Clinical Tuberculosis 5th Edition 2014 p 211
Eur Respir J. 2011 Feb;37(2):441-62.

Isoniazid (INH)

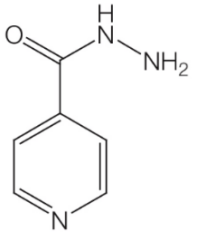


Figure 123.1. Chemical structure of isoniazid (isonicotinic acid hydrazide).

- Inhibits mycolic acid synthesis

- INH is a prodrug that is converted by the mycobacterial enzyme catalase peroxidase (***katG***) into active form, then inhibits the product of the ***inhA*** gene.

"Profound early bactericidal activity…" Accounts for the majority of early bactericidal activity of multidrug TB regimens

  - No sterilizing activity. Prevents resistance.
  - Excellent absorption and tissue penetration

- Adults: 5 mg/kg (300 mg/daily), 15 mg/kg (900 mg) twice or three times weekly

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

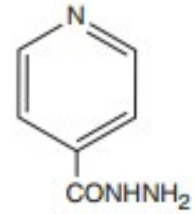
(1) Ann Intern Med. 1978 May;88(5):650-2.

INH Hepatotoxicity

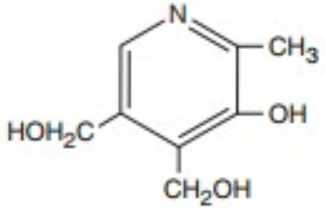
- Mechanisms: unknown
- Asymptomatic elevation of aminotransferases: 20% of patients
- Clinical hepatitis: 0.6% of patients
- Fulminant hepatitis (hepatic failure): Approximately 4/100,000.

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

INH Peripheral Neurotoxicity



Isoniazid

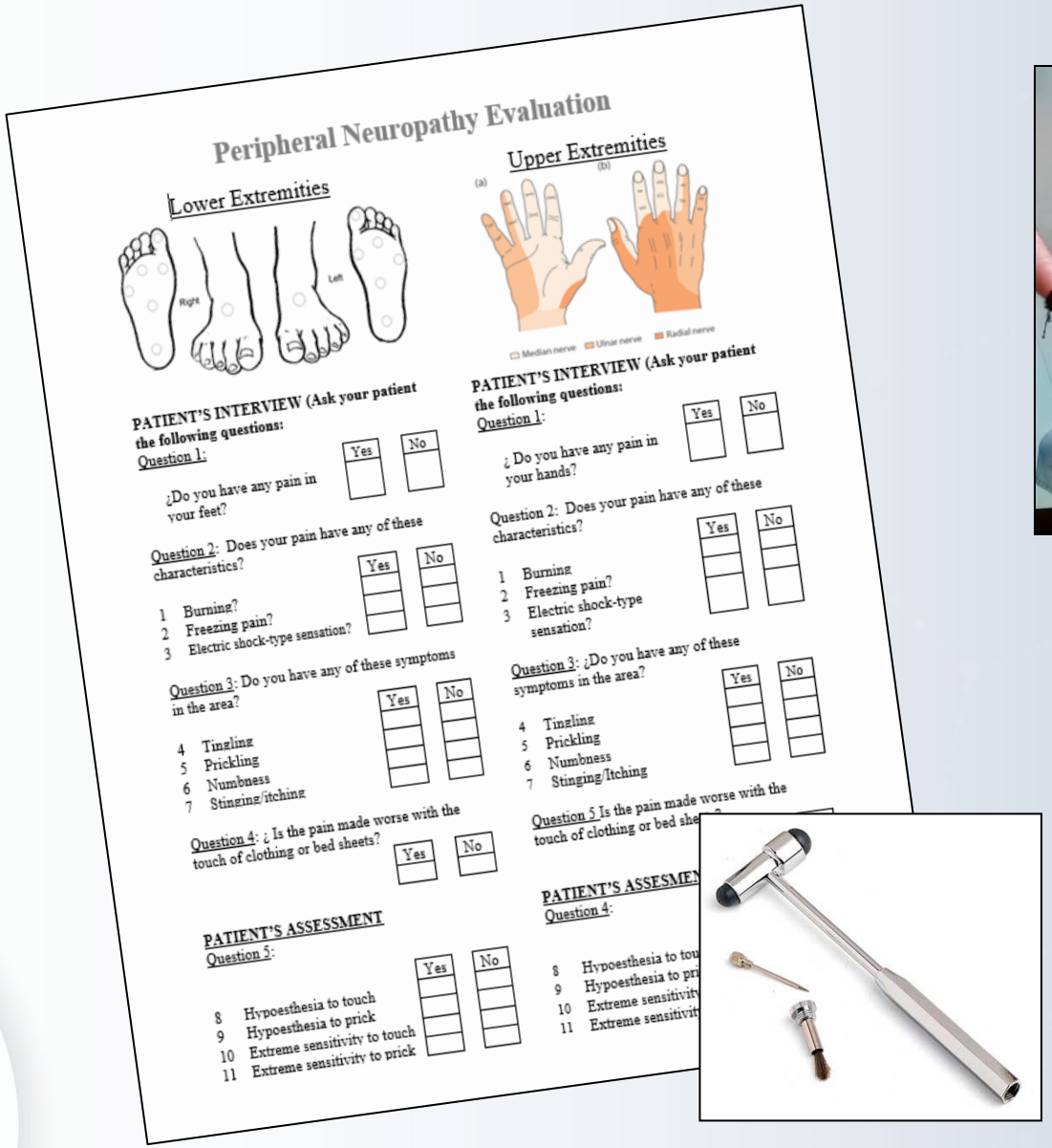


Pyridoxine

- Dose Related, Functional vitamin B6 deficiency (blocking conversion of B6 to pyridoxal phosphate/enhance excretion)
- 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)

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



Peripheral Neuropathy Evaluation

Lower Extremities

Right

Left

Upper Extremities

(a) (b)

Median nerve Ulnar nerve Radial nerve

PATIENT'S INTERVIEW (Ask your patient the following questions:

Question 1:

¿Do you have any pain in your feet?

Yes	No

Question 2: Does your pain have any of these characteristics?

	Yes	No
1 Burning?		
2 Freezing pain?		
3 Electric shock-type sensation?		

Question 3: Do you have any of these symptoms in the area?

	Yes	No
4 Tingling		
5 Prickling		
6 Numbness		
7 Stinging/itching		

Question 4: ¿ Is the pain made worse with the touch of clothing or bed sheets?

Yes	No

PATIENT'S ASSESSMENT

Question 5:

	Yes	No
8 Hypoesthesia to touch		
9 Hypoesthesia to prick		
10 Extreme sensitivity to touch		
11 Extreme sensitivity to prick		

PATIENT'S INTERVIEW (Ask your patient the following questions:

Question 1:

¿ Do you have any pain in your hands?

Yes	No

Question 2: Does your pain have any of these characteristics?

	Yes	No
1 Burning		
2 Freezing pain?		
3 Electric shock-type sensation?		

Question 3: ¿Do you have any of these symptoms in the area?

	Yes	No
4 Tingling		
5 Prickling		
6 Numbness		
7 Stinging/Itching		

Question 5 Is the pain made worse with the touch of clothing or bed she

PATIENT'S ASSESSMEN

Question 4:

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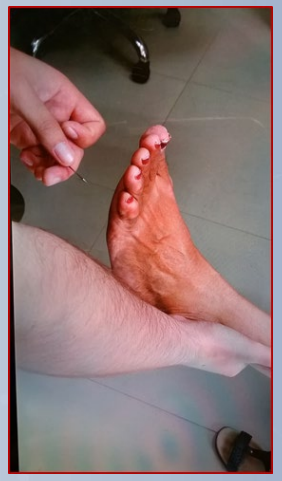
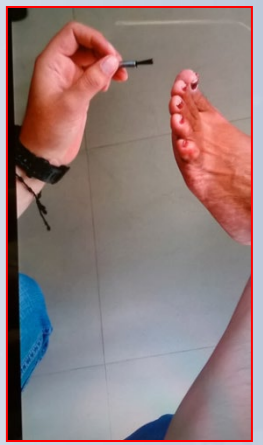




RIFAMPIN (RIF)

(Rifamycins: rifampin, rifabutin, rifapentine)

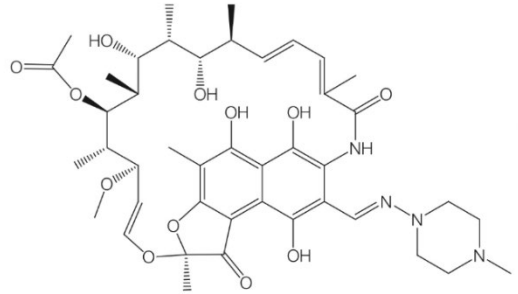


Figure 126.1. Chemical structure of rifampicin.

- Bactericidal/**highest sterilizing activity**. Activity against rapidly dividing and against **semi-dormant bacterial** populations.
- **Cornerstone** of short course therapy
- Single mutations in *rpoB* gene (Beta subunits of RNA polymerase.)

- Well absorbed, good tissue levels
- Adults: 10 mg/kg (600 mg) daily, twice weekly or three times weekly (dosing of rifampin being re-evaluated)

- Recent Study: 20 – 35+ mg/kg daily seem to be safe with an increased efficacy.(1, 2)

(1) Am J Respir Crit Care Med. 2018 Sep 1;198(5):657-666
(2) PLoS One. 2019 Mar 14;14(3):e0213718

Rifampin Toxicity

- **Well tolerated medication: Only 1.9% have 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

Rifampin Toxicity

- Flu-like 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)

Rifapentine

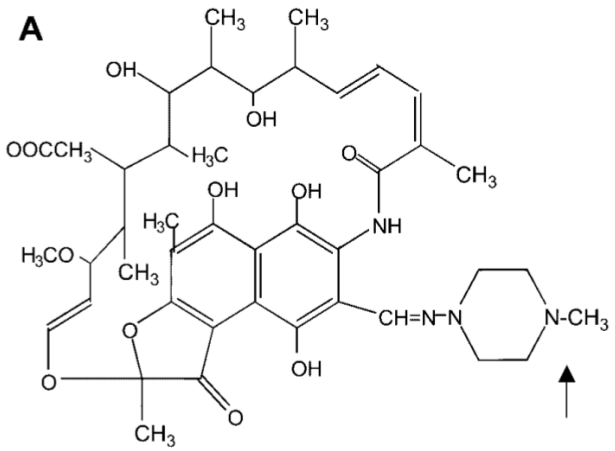
- CDC recommends **3HP for latent TB**.
- Long acting rifamycin is highly protein bound that can be used once weekly with INH for latent TB therapy.
- Interim CDC guidance: A part of **4 month regimen** for active Tb. (1)
- Adverse effects similar to rifampin

- For latent tuberculosis, better completion rate.
- Resistance: *rpoB*

Pill Burden & Price

- For 3HP: 900mg (6 pills) + companion drugs (4 pills)
- For HMPZ: 1200 mg (8 pills) + companion drugs (5-7 pills)

(1) CDC Interim Guidance 2022
(2) IDSA 2016 guideline



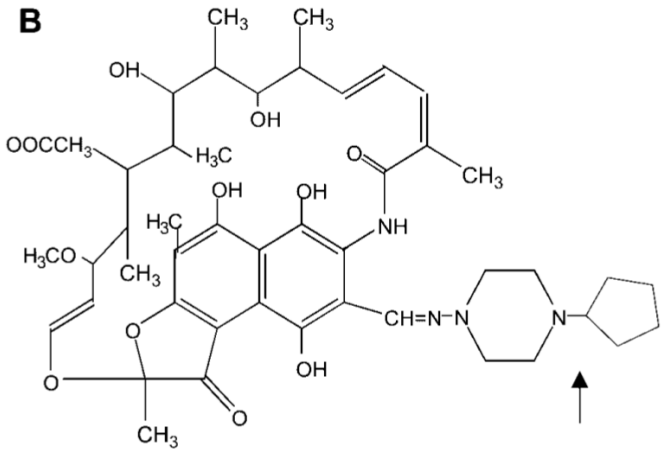


Table 1. Comparing features of rifampin versus rifapentine.

	Rifampin	Rifapentine
MIC	0.125–0.25 µg/mL	0.01–0.06 µg/mL
Half-life	2 h	15 h
Protein binding	80–85%	97–99%
Food requirement	No	Yes
Kinetic	Nonlinear (Michaelis–Menten)	Nonlinear (saturable absorption)
Hepatic enzyme induction	3-fold	4.5-fold
Flat vs. mg/kg dosing	mg/kg	Flat
Cavitary penetration	Good	Poor
Access	Global	Limited
Efficacy	Comparative efficacy at high doses is to be determined	

MIC: Minimum inhibitory concentration.

Expert Rev Clin Pharmacol. 2017 Oct;10(10):1027-1036.

Rifabutin

- A substitute for rifampin for patients who are receiving drugs, especially antiretroviral drugs, that have unacceptable interactions with rifampin.

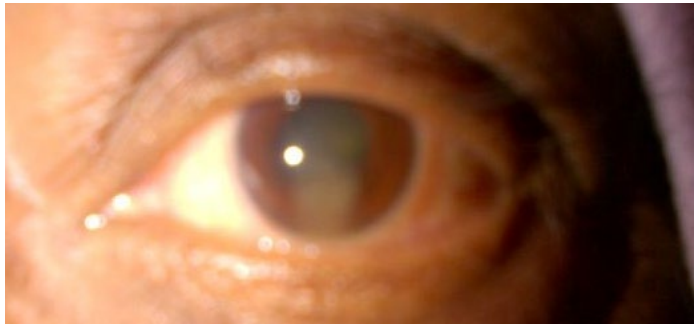
- **Less severe induction of hepatic microsomal enzymes than rifampin**, therefore, less effect on the metabolism of other drugs

- Adult dose 5 mg/kg (300 mg daily).

IDSA 2016 guideline

Rifabutin Toxicity

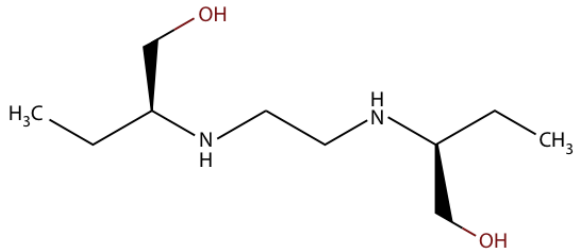
- Hematologic toxicity: **neutropenia** and thrombocytopenia
- **Drug interactions: less severe than rifampin:**
  - Still requires dose adjustment: e.g. tacrolimus (1)
- Uveitis: Rare, < 0.01% (Combination with macrolides)
- GI Symptoms
- Polyarthralgia: 1-2% at standard doses
- Pseudojaundice (HIV,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



Transpl Infect Dis . 2022 Aug;24(4):e13893

ETHAMBUTOL

Ethambutol (EMB)



- Included in first-line treatment regimens to prevent the **emergence of Rif resistance** when INH resistance may be present. Bacteriostatic activity; little to no sterilizing activity

- Adults: 15 mg/kg daily (See table in IDSA guideline 2016.)

TABLE 5. Suggested ethambutol doses, using whole tablets, for adults weighing 40–90 kilograms

	Weight (kg)*		
	40–55	56–75	76–90
Daily, mg (mg/kg)	800 (14.5–20.0)	1,200 (16.0–21.4)	1,600† (17.8–21.1)
Thrice weekly, mg (mg/kg)	1,200 (21.8–30.0)	2,000 (26.7–35.7)	2,400† (26.7–31.6)
Twice weekly, mg (mg/kg)	2,000 (36.4–50.0)	2,800 (37.3–50.0)	4,000† (44.4–52.6)

* Based on estimated lean body weight.
† Maximum dose regardless of weight.

IDSA 2016 guideline

Ethambutol 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

Ethambutol 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.

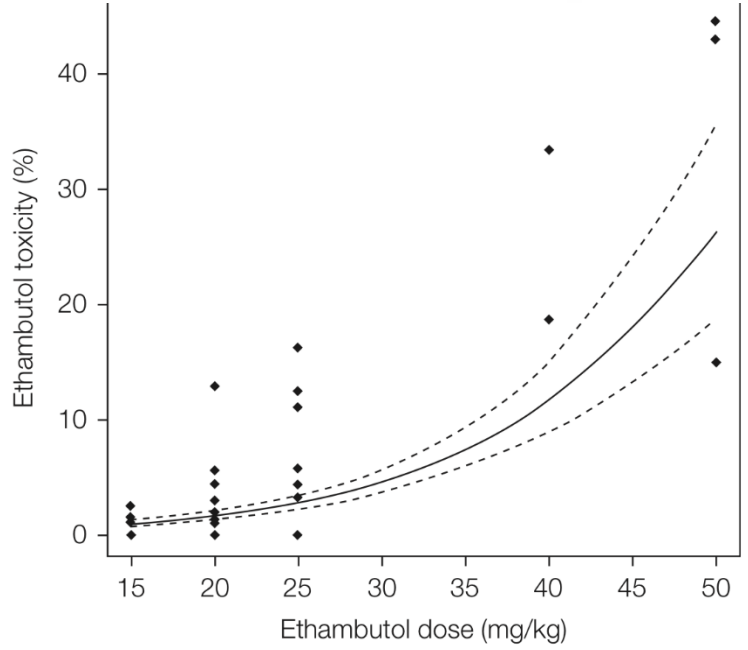
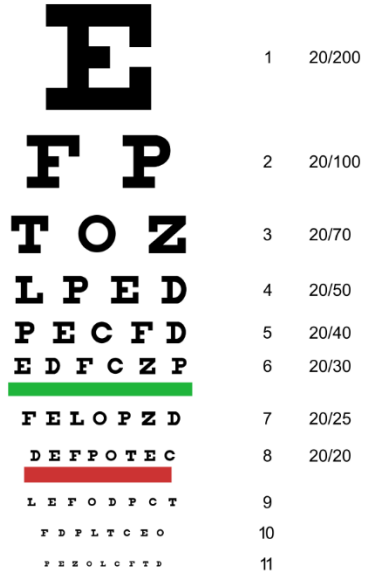


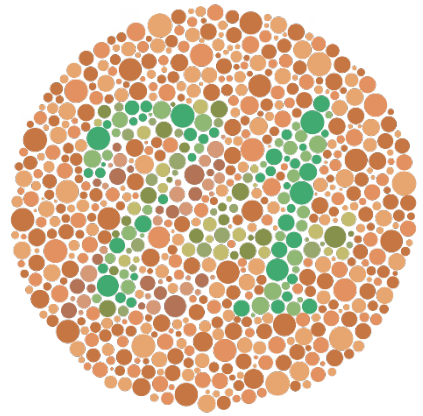
Figure 124.2. Ocular toxicity and dose of ethambutol. $y = \exp(-6.0599 + 0.l006*\text{dose})/(l + \exp(-6.0599 + 0.l006*\text{dose}))$. The broken lines represent the 95% confidence interval limits. (From WHO, 2006.)

Kucers' The Use of Antibiotics 7th

Ethambutol 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)
- Close monitoring: high doses, treatment longer than 2 months, renal insufficiency
- Ophthalmology evaluation, no single diagnostic test for ethambutol ocular toxicity

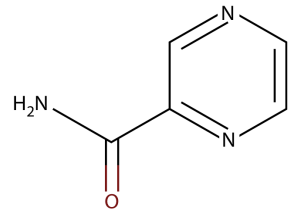


Ethambutol Ocular Toxicity

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)



- Bacteriostatic/**sterilizing agent**: Greatest activity against dormant or semi-dormant (slowly growing) organisms within macrophages or caseous foci (acidic environment).
- Not preventing resistance
- Six month treatment regimen depends on the use of PZA for the initial 2 months

- Adults: 20-25 mg/kg (2.0 g) daily, (See table IDSA Guideline 2016)

TABLE 4. Suggested pyrazinamide doses, using whole tablets, for adults weighing 40–90 kilograms

	Weight (kg)*		
	40–55	56–75	76–90
Daily, mg (mg/kg)	1,000 (18.2–25.0)	1,500 (20.0–26.8)	2,000† (22.2–26.3)
Thrice weekly, mg (mg/kg)	1,500 (27.3–37.5)	2,500 (33.3–44.6)	3,000† (33.3–39.5)
Twice weekly, mg (mg/kg)	2,000 (36.4–50.0)	3,000 (40.0–53.6)	4,000† (44.4–52.6)

*Based on estimated lean body weight.
†Maximum dose regardless of weight.

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

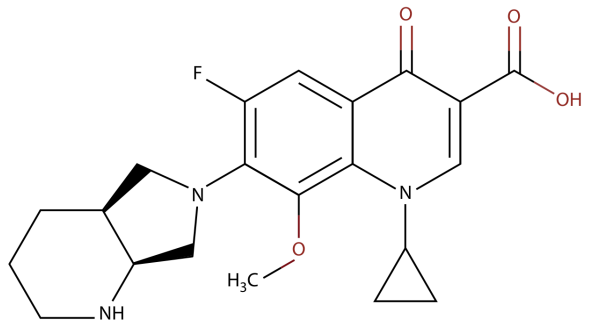
Fluoroquinolones

- Inhibit DNA gyrase and Topoisomerase IV
- Levofloxacin and Moxifloxacin

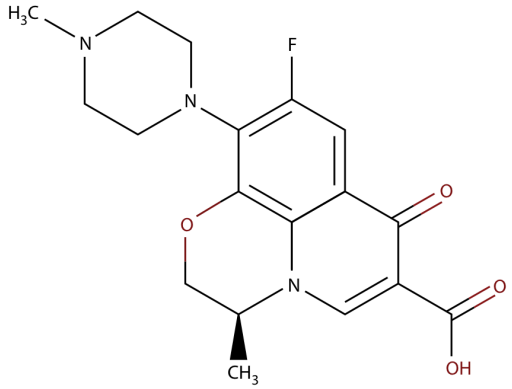
- Oral bioavailability > 90%
- MFX: 400mg daily, and up to 800mg
- LFX: 750mg daily up to 1000mg

Ofloxacin: approved for use in the United States in 1990, but was discontinued by its initial sponsor in 2009, partially because of the frequency of adverse side effects.

MOXIFLOXACIN



LEVOFLOXACIN



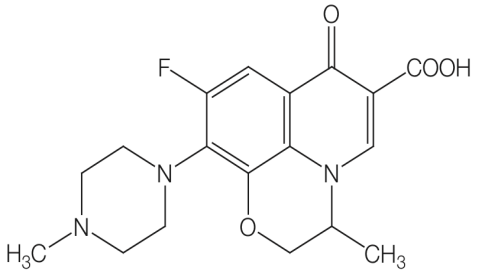


Figure 103.1. Chemical structure of ofloxacin.

Adverse Effects of Fluoroquinolones

- **Gastrointestinal disturbance:** nausea/bloating 0.5-2%
- **QTc Prolongation**
  - MFX: 6.4 - 14.9 ms at Cmax
  - LFX: 6ms
- **Tendinopathy**
- LFX: higher risk of **tendinopathy** and **tendon rupture**
- **CNS toxicity**
- Psychiatric disturbance/lower seizure threshold

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

Side Effects of First Line Drugs

Isoniazid	Rifampin	Rifabutin
• G.I. upset • Rash • Hepatotoxicity • Peripheral neuropathy	• G.I. upset • Rash • Hepatotoxicity • Thrombocytopenia, hemolytic anemia • Renal toxicity • Flu-like syndrome • Orange staining of body fluids	• Rash/Skin discoloration • Hepatotoxicity • Leukopenia • Thrombocytopenia • Uveitis • Arthralgias
Pyrazinamide	**Ethambutol**	
• G.I. upset • Rash • Hepatotoxicity • Arthralgias • Gout (rare)	• Optic Neuritis • Rash	

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

Drug	Dose (mg/kg)	Rash	Hepatitis	GI
INH	5.2	1.5	1.8	1.6
RIF	10.2	3	0	1.3
PZA	24.2	6	5.2	2.1
EMB	16.8	0	0	0

Incidence is expressed as events per 1000 person-months of treatment.

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

Gastrointestinal Upset

- Common in the first few weeks of therapy
- **Always rule out hepatotoxicity**.

- **Frequency**: pyrazinamide > isoniazid > rifampin/quinolones > ethambutol & aminoglycosides

- **Initial options**
  - Change the timing of the meds, w/ snacks or foods
  - Daily dosing with fewer pills if intermittent
  - Antacids 2hrs before or after
  - Anxiolytic if due to pill burden
  - Antiemetics

Treatment Options for GI Upset

- **Antiemetics options**
  - Ondansetron (Zofran) 4-8mg po prn
  - Promethazine (Phenergan) 12.5 to 2mg q6 prn
  - Prochlorperazine (Compazine) 5 – 10 mg q6hr prn
  - Hydroxyzine (Atarax) 25 – 50 mg q6hr

- **Other consideration**
  - Stop EMB if pansusceptible
  - Discontinue PZA
  - If severe, hold meds and rechallenge one by one

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.
- Bili/INR/APTT

Management of Hepatotoxicity

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

     OR

  2. ALT or AST > 5 times w/o symptoms

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

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

Hepatotoxicity – What to do about it

- First, can treatment be stopped safely?
  - Is the patient really sick (ICU, septic sick)?
  - Do they have a form of TB you really don't want going untreated (disseminated disease, meningitis, associated with HIV or poorly controlled diabetes)?
- If the patient is ill, pick something liver-sparing and continue treatment.
- If the patient is stable, stop the medications until the liver cools off and do a drug challenge.

What if they are really, really sick……?

• INH	• Liver
• Rifampin	• Liver
• Rifabutin	• Liver/kidney
• Ethambutol (EMB)	• Kidney
• Pyrazinamide (PZA)	• Kidney (liver metabolites)
• Moxifloxacin ←	• Liver, but…….
• Levofloxacin	• Kidney
• Amikacin ←	• Kidney
• Linezolid ←	• Neither liver or kidney

Liver sparing but not dying

• INH	• Liver
• Rifampin	• Liver
• Rifabutin	• Liver/kidney
• Ethambutol (EMB) ←	• Kidney
• Pyrazinamide (PZA)	• Kidney (liver metabolites)
• Moxifloxacin ←	• Liver, but…….
• Levofloxacin	• Kidney
• Amikacin	• Kidney
• Linezolid ←	• Neither liver or kidney

Liver-friendly

• INH		• Liver
• Rifampin	←	• Liver
• Rifabutin		• Liver/kidney
• Ethambutol (EMB)	←	• Kidney
• Pyrazinamide (PZA)		• Kidney (liver metabolites)
• Moxifloxacin	←	• Liver, but…….
• Levofloxacin		• Kidney
• Amikacin		• Kidney
• Linezolid		• Neither liver or kidney

What is a proper ‘drug challenge’?

- Stop the medications. Cool the patient off.
- When LFTs have returned to < 2 times the ULN, you are ready to challenge
- Start with rifampin and ethambutol, then INH, then strongly consider whether you need PZA
  - Wait 3-7 days between additions
  - Check LFTs before starting the next drug (and wait for the results, please)
  - If LFTs rise stop the last drug added and go to the next

Rifabutin

- Rifabutin can be substituted for rifampin. (Not FDA Approved)
- Many tolerate rifabutin if rifampin intolerance.
- Still can cause drug induced liver injury though MUCH less likely

Antimicrob Chemother. 2014 Mar;69(3):790-6

Rash

- All Mtb meds can cause rash.

- Consider other causes
  - Other medications, new soaps/detergents
  - Insect bites (bed bugs), Xerosis, Herpes Zoster and Scabies

Management of Rash

- **Minor rash or itching**
  - Flushing: PZA or RIF
  - Manage symptomatically with antihistamines or topical steroid
  - Continue meds

- **Petechiae**
  - Check for 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

TB drugs and renal diseases

- Decreasing the dose of Mtb drugs in patients with renal disease is NOT the best method of treating tuberculosis

- The peak serum concentrations may be too low. Instead, increasing the dosing interval is recommended.

IDSA Guideline 2016

Dose Adjustment

Table 12. Dosing Recommendations for Adult Patients With Reduced Renal Function[a]

Drug	Change in Frequency?	Recommended Dose and Frequency for Patients With Creatinine Clearance <30 mL/min, or Patients Receiving Hemodialysis
Isoniazid	No	300 mg once daily, or 900 mg 3 times/wk
Rifampin	No	600 mg once daily, or 600 mg 3 times/wk
Pyrazinamide	Yes	25–35 mg/kg/dose 3 times/wk (not daily)
Ethambutol	Yes	20–25 mg/kg/dose 3 times/wk (not daily)
Levofloxacin	Yes	750–1000 mg/dose 3 times/wk (not daily)
Moxifloxacin	No	400 mg once daily
Cycloserine	Yes	250 mg once daily, or 500 mg/dose 3 times/wk[b]
Ethionamide	No	250–500 mg/dose daily
Para-amino salicylic acid	No	4 g/dose twice daily
Streptomycin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)
Capreomycin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)
Kanamycin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)
Amikacin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)

- Standard doses are given unless there is intolerance.
- The medications should be given after hemodialysis on the day of hemodialysis.
- Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.
- Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing using serum concentration monitoring.
- In patients with 30–50 mL/min creatinine clearance, standard doses are used by experts, but measurement of serum concentrations 2 and 6 hours after timed administration can be used to assist with optimizing drug dosages.

The meds should given after hemodialysis on the day of hemodialysis.
Monitoring of serum drug concentrations should be considered
No data available for peritoneal dialysis

INH and RIF do not need dose adjustment

IDSA Guideline 2016

Liver disease and Tuberculosis

- Risk factors – advanced liver disease, liver transplant and Hep C infections, baseline ALT abnormalities.

- Latent Tuberculosis Infection

  - Use liver friendly regimens

  - If liver transplant candidates, consider rifampin or deferring treatment to post-liver transplant if the patient may not tolerate.

IDSA Guideline 2016

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

Isoniazid

- Interacts with anticonvulsants, like phenytoin
- Plavix

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/
- https://www.drugs.com/drug_interactions.html

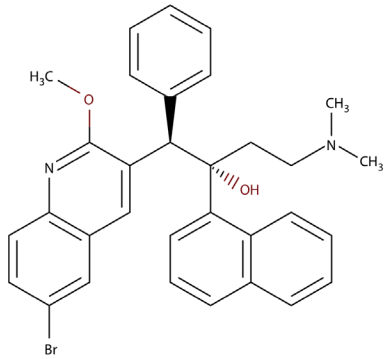
HIV meds

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

Second Line TB Drugs

Bedaquiline

BEDAQUILINE



- 2012 Bedaquiline FDA approved for treatment of drug resistant TB, only with pretomanid and linezolid

- Weeks 1 – 2: 400 mg (4 tablets of 100 mg) given orally, once daily
- Weeks 3 – 24: 200 mg (2 tablets of 100 mg) three times per week, for a total dose of 600 mg per week with foods*

*Increased two-fold by food

Bedaquiline

- Bedaquiline acts on both actively replicating and dormant mycobacteria by inhibiting mycobacterial ATP synthase, a unique antimycobacterial mechanism
- There is no cross-resistance between bedaquiline and other anti-TB drugs, **except for clofazimine**, possibly via upregulation of a multisubstrate efflux pump (*Rv0678*)
- There are concerns about QT interval prolongation, unexplained association with death. Initial concerns about sudden death with bedaquiline **NOT** confirmed
- Good treatment responses and safety profiles
- Dose adjustment is not required in case of mild-to-moderate renal impairment

Bedaquiline: Side Effects

- Nausea (35%)

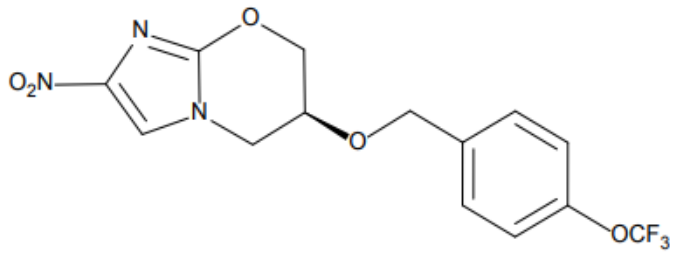
  First two weeks, usually they develop GI symptoms, but better after decreasing the doses

- QT prolongation: 9% increased > 60ms
- ECG should be obtained before initiation, & at least 2, 12 & 24 weeks after starting treatment.

- Headache (23.5%)
- Arthralgia (29.4%)
- Increase in LFTS/amylase

MMWR: Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis

Pretomanid



- 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

- Owing to similar structure, pretomanid shares cross-resistance with delamanid as well as a relatively **high propensity to acquiring bacillary drug resistance**

- FDA approved in 2019 with combination (BPaL) for pulmonary XDR/MDR TB in the U.S.

Drug Drug Interaction

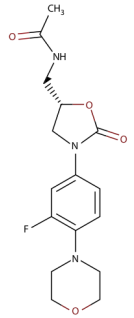
- Efavirenz reduces pretomanid exposure
- Dolutegravir based HIV treatment regimens: No interaction

Pretomanid: Potential Side Effects

Data from BPaL (Nix-TB trial)

- Hepatic adverse reactions
- Myelosuppression
- Peripheral and optic neuropathy
- QT prolongation
- Reproductive effects
- Lactic acidosis

Linezolid: Oxazolidinone



- Inhibit protein synthesis by binding to the ribosomal 50S subunit.
- Oxazolidinone antibiotic: inhibits protein synthesis by a mechanism not shared by other antibiotics

- Does not induce nor is significantly metabolized by cytochrome P450 enzymes
- Excellent penetration into bronchial mucosa and bronchioalveolar fluid
- Does not require dosage adjustment with renal insufficiency
- Very active in vitro against drug susceptible and drug resistant MTB
- Can be given orally

Linezolid: Adverse Effects

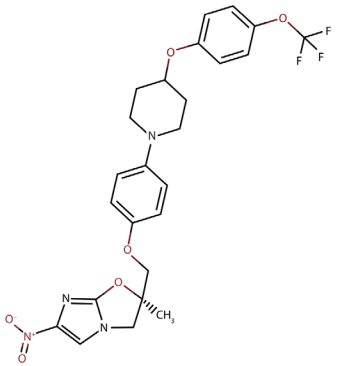
- **Serotonin Syndrome (avoid giving with serotonergic agents)**

- **Mitochondria Toxicity**
  - **Bone marrow suppression** - dose dependent/reversible
  - **Peripheral Neuropathy** - Not dose dependent (? not reversible): 12-20 weeks of treatment, role of trough <2.0?
  - **Optic neuritis:** may be rechallenged?
  - Hyperlactatemia
  - GI disturbance
  - Rash

Treatment of Drug-Resistant Tuberculosis An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

DELAMANID

Delamanid



- Delamanid is a derivative of a nitro-dihydro-imidazooxazole derivative
- Inhibits mycolic acid biosynthesis, with excellent activity against intracellular MTB
- Not approved by FDA (Compassionate use)

Delamanid: Side Effects

- **QT prolongation**

  Mean change in QTcF

  - 11.9 ms in the bedaquiline arm
  - 8.6 ms in the delamanid arm
  - 20.7 ms in the combined arm

(1) QT effects of bedaquiline, delamanid or both in MDR-TB patients: the deliberate trial

Toxicity Monitoring 2nd Line TB Drugs

- **TSH**, baseline and q 3 months: ethionamide, PAS
- **VA/color vision baseline and follow-up**: clofazimine, linezolid
- **EKG baseline and follow-up**: bedaquiline, clofazimine
- **CBC** baseline and monthly: linezolid
- **Mg**: Amikacin, Streptomycin, Capreomycin
- **Auditory and Vestibular testing baseline and follow-up**: Amikacin, Streptomycin, Capreomycin
- **Routine Serum drug levels**: Cycloserine
- **Routine Psychiatric assessment**: Cycloserine
- **Routine Neuropathy assessment**: Linezolid, Ethionamide, Cycloserine

QT interval prolongation

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

Questions?