



Tuberculosis Drugs

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Clinical Management of TB for Physicians • August 25, 2026 • San Antonio, Texas

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Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity





Tuberculosis Drugs

First line Drugs

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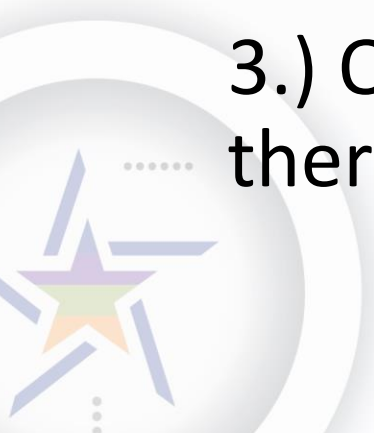
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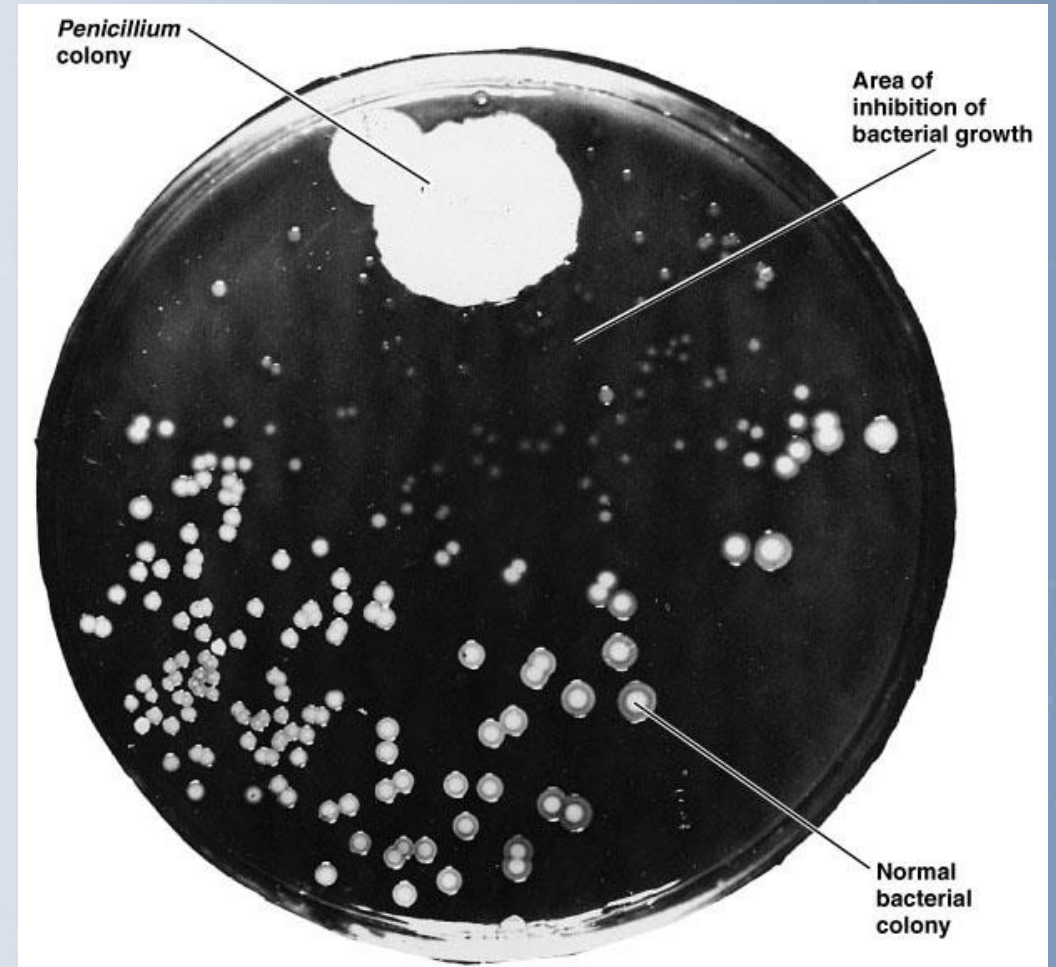


Objectives

- 1.) Outline the current first-line drugs used to combat TB infection and TB disease.
- 2.) Describe the common adverse effects of TB treatment regimens and how to manage them.
- 3.) Outline the current second-line drugs used for interim therapy due to toxicity of first-line drugs.



- **1928** – Fleming discovered penicillin, produced by *Penicillium*.
- **1940** – Howard Florey and Ernst Chain performed first clinical trials of penicillin.
- **1943** -Albert Schatz (Selman Waksman, 1952 Nobel) discovered **streptomycin**
- **1951** – **Isoniazid** discovered
- **1952** – **Pyrazinamide** discovered
- **1957** – **Rifampin** discovered (1971)
- **1961** – **Ethambutol** discovered
- **2012** – Bedaquiline FDA approved (discovered 1997)
- **2019** – Pretomanid FDA approved



ANTITUBERCULOSIS 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 the 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

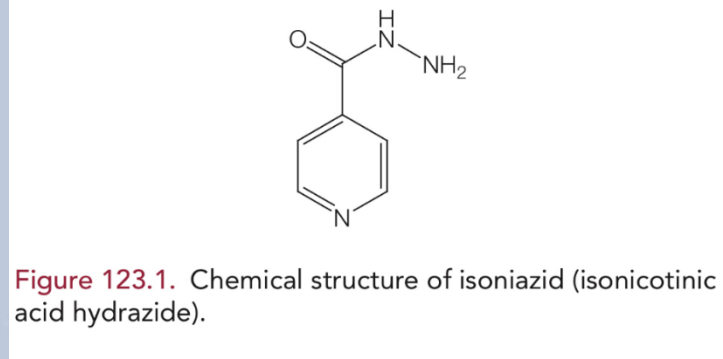


Terminology for Mtb PK/PD

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



Isoniazid (INH)



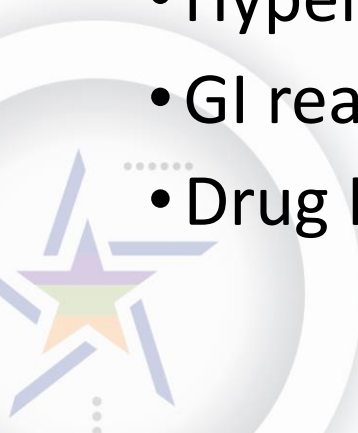
- Inhibits mycolic acid synthesis
- INH is a prodrug that is converted by the mycobacterial enzyme catalase peroxidase (***katG***) into active form, then inhibits the product of the ***inhA*** gene.

“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

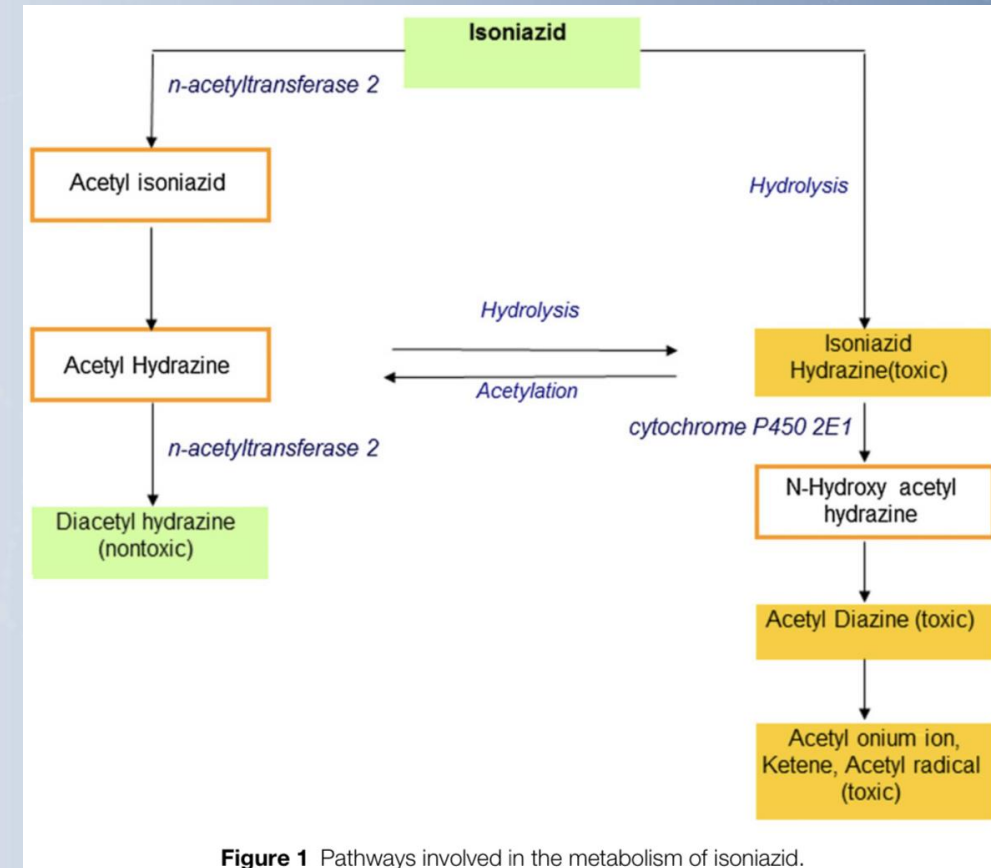
INH Toxicity

- **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



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.

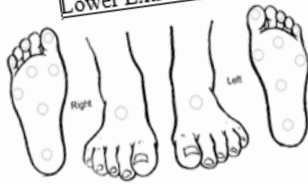


INH Peripheral Neurotoxicity

- 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)

Peripheral Neuropathy Evaluation

Lower Extremities



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?

- 1 Burning?
- 2 Freezing pain?
- 3 Electric shock-type sensation?

Yes	No
☐	☐
☐	☐
☐	☐

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

- 4 Tingling
- 5 Prickling
- 6 Numbness
- 7 Stinging/itching

Yes	No
☐	☐
☐	☐
☐	☐
☐	☐

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

Yes	No
☐	☐

PATIENT'S ASSESSMENT

Question 5:

- 8 Hypoesthesia to touch
- 9 Hypoesthesia to prick
- 10 Extreme sensitivity to touch
- 11 Extreme sensitivity to prick

Yes	No
☐	☐
☐	☐
☐	☐
☐	☐

Upper Extremities



□ Median nerve □ Ulnar nerve □ Radial nerve

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?

- 1 Burning
- 2 Freezing pain?
- 3 Electric shock-type sensation?

Yes	No
☐	☐
☐	☐
☐	☐

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

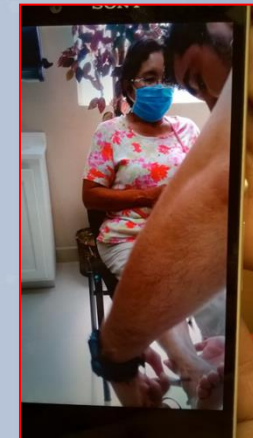
- 4 Tingling
- 5 Prickling
- 6 Numbness
- 7 Stinging/itching

Yes	No
☐	☐
☐	☐
☐	☐
☐	☐

Question 5: Is the pain made worse with the touch of clothing or bed sheets?

PATIENT'S ASSESSMENT
Question 4:

- 8 Hypoesthesia to touch
- 9 Hypoesthesia to prick
- 10 Extreme sensitivity to touch
- 11 Extreme sensitivity to prick



MONITOR ALL THE
DANGER SIGNS.

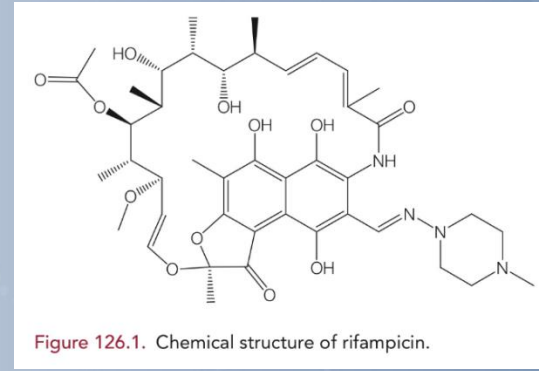


© 2007 Diabetes Health



RIFAMPIN (RIF)

(Rifamycins: rifampin, rifabutin, rifapentine)



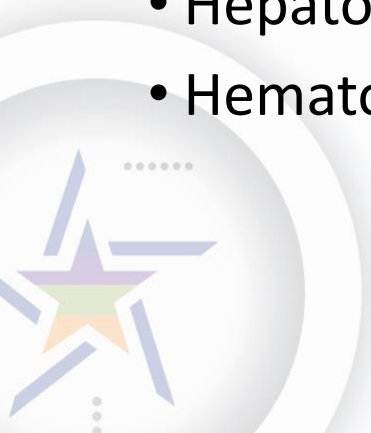
- Bactericidal/highest sterilizing activity. Activity against rapidly dividing and against semi-dormant bacterial populations.
- Cornerstone of short course therapy
- Single mutations in *rpoB* gene (Beta subunits of RNA polymerase.)
- Well absorbed, good tissue levels
- Adults: 10 mg/kg (600 mg) daily, 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

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



RIF 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

- Current: 10 pills rifapentine 900mg (6 pills), INH (3 pills) and vit B6

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).

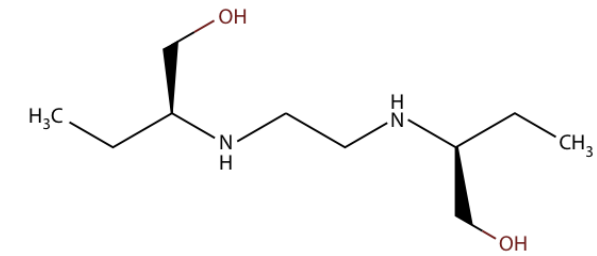


Rifabutin Toxicity

- 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



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.

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.

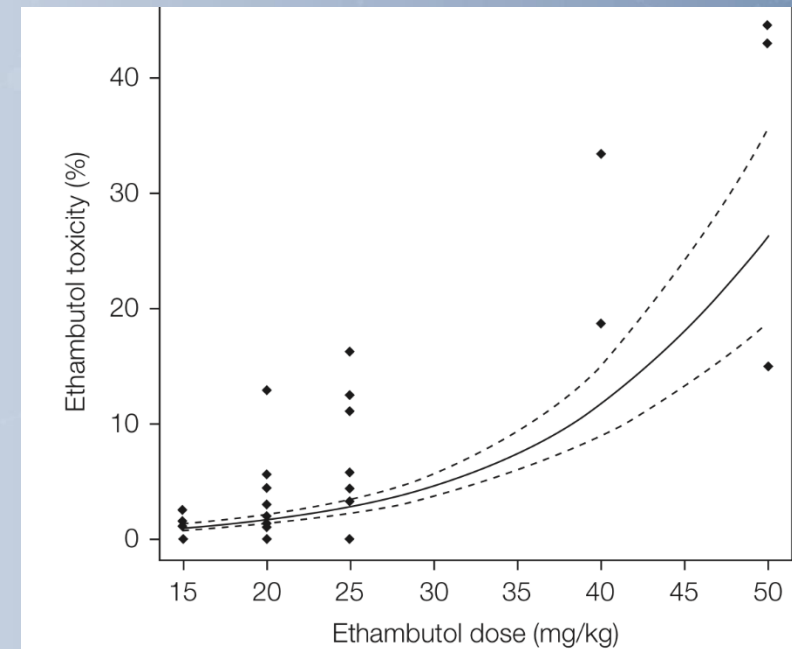


Figure 124.2. Ocular toxicity and dose of ethambutol. $y = \exp(-6.0599 + 0.1006 \cdot \text{dose}) / (1 + \exp(-6.0599 + 0.1006 \cdot \text{dose}))$. The broken lines represent the 95% confidence interval limits. (From WHO, 2006.)

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



EMB Ocular Toxicity

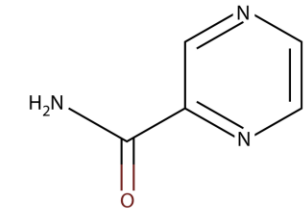
Management

- Discontinue EMB immediately
- If severe, consider discontinuing EMB & INH

Recovers over weeks to months, but defective color vision may persist longer.

- Refer to ophthalmology





- 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

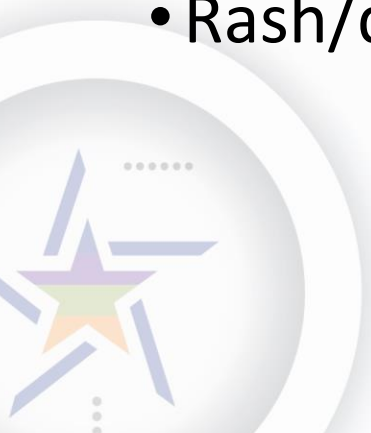
	Weight (kg)*		
	40–55	56–75	76–90
Daily, mg (mg/kg)	1,000 (18.2–25.0)	1,500 (20.0–26.8)	2,000† (22.2–26.3)
Thrice weekly, mg (mg/kg)	1,500 (27.3–37.5)	2,500 (33.3–44.6)	3,000† (33.3–39.5)
Twice weekly, mg (mg/kg)	2,000 (36.4–50.0)	3,000 (40.0–53.6)	4,000† (44.4–52.6)

* 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

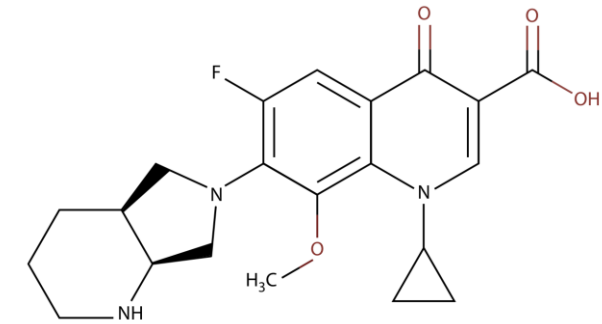


Fluoroquinolones

- 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

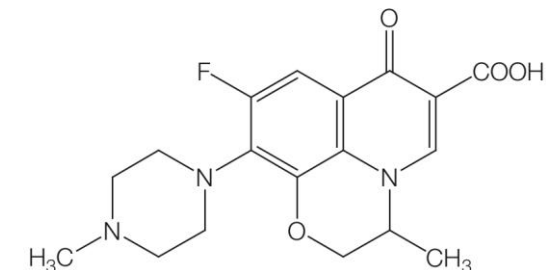
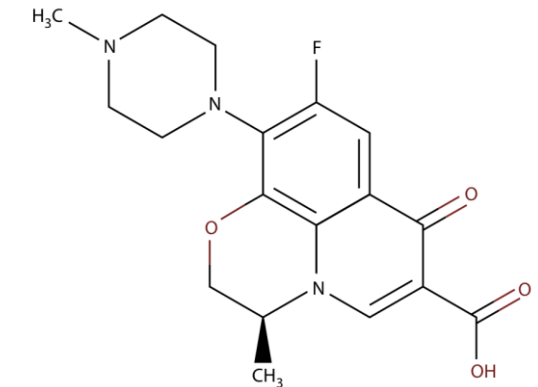


Figure 103.1. Chemical structure of ofloxacin.

Adverse Effects of FQN

Gastrointestinal disturbance: nausea/bloating 0.5-2%

QTc Prolongation

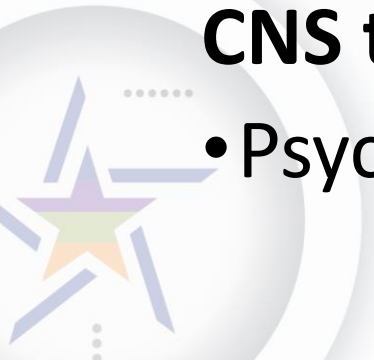
- MFX: 6.4 - 14.9 ms at C_{max}
- LFX: 6ms

Tendinopathy

- LFX: higher risk of **tendinopathy** and **tendon rupture**

CNS toxicity

- Psychiatric disturbance/lower seizure threshold



Fluoroquinolone Toxicity

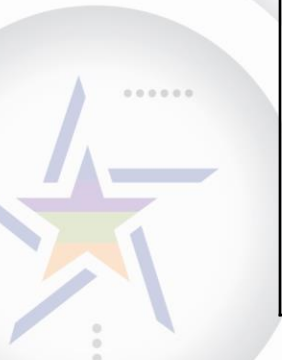
Musculoskeletal

- 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

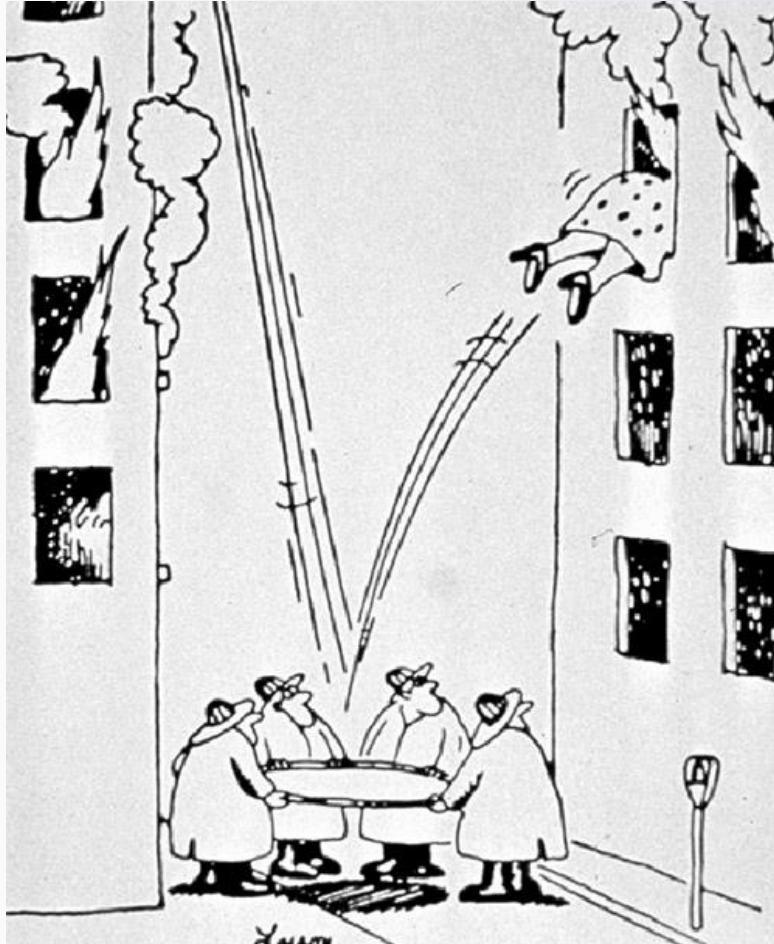


Side Effects of First Line Drugs

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



Common Adverse Effects



Sometimes our interventions can be dangerous...



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

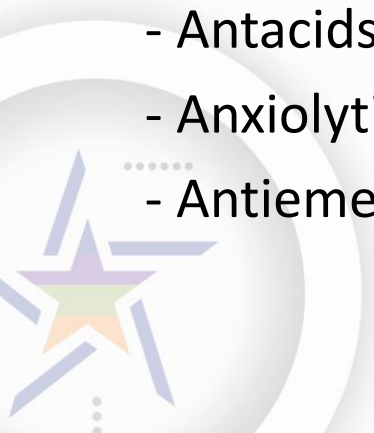
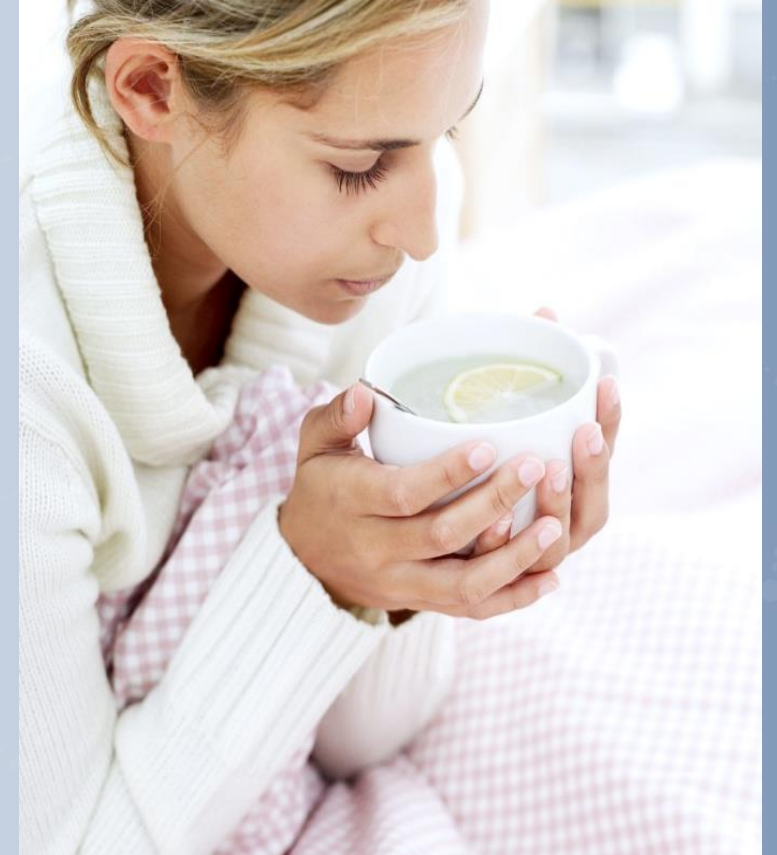
Incidence is expressed as events per 1000 person-months of treatment.

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.
(Consultation)



Risk Factors for Hepatotoxicity

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

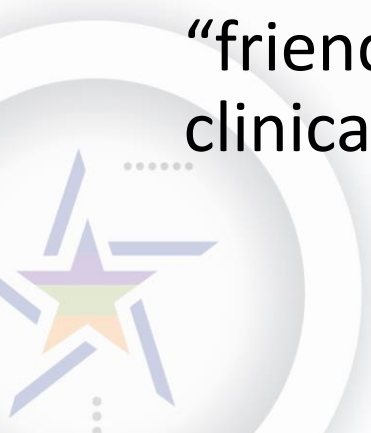
Monitoring Hepatotoxicity

- 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



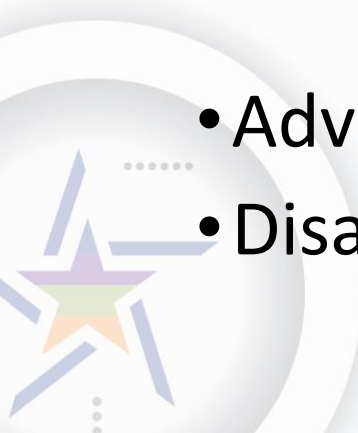
Management

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



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: may elect not to restart PZA
- Advantage: 2 most potent TB drugs
- Disadvantages: 9 month regimen, still potentially hepatotoxic



Rifabutin

- Rifabutin can be substitute for rifampin. (Not FDA Approved)
- Many tolerate rifabutin on rifampin intolerance. (1)
- Still can cause drug induced liver injury.



(1)J 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



- **Minor rash or itching**

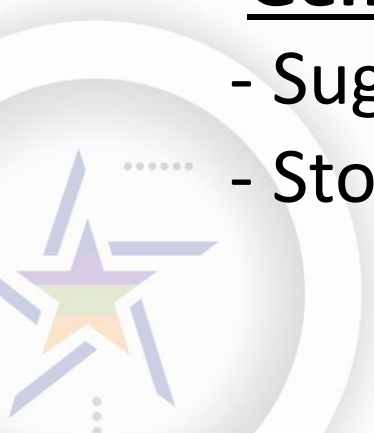
- Flushing: PZA or RIF
- Manage symptomatically with antihistamines or topical steroid
- Continue meds

- **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



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.



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)

The meds should be given after hemodialysis on the day of hemodialysis.

Monitoring of serum drug concentrations should be considered

No data available for peritoneal dialysis

RIF does not need dose adjustment (vs. package Insert.)

Liver disease and Tuberculosis

- Risk factors – advanced liver disease, liver transplant and Hep C infections, baseline ALT abnormalities.
- Latent Mtb
 - Use liver friendly regimens
 - If liver transplant candidates, consider rifampin or deferring treatment to post-liver transplant if the patient may not tolerate.



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

Interact with anticonvulsant, like phenytoin



Common Rifampin Drug Interactions

IMPOSSIBLE TO REMEMBER ALL

Remember potential life threatening int.

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

Useful Websites

- Lexicomp®
- <https://www.wolterskluwer CDI.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>



Tuberculosis Drugs

Second line Drugs

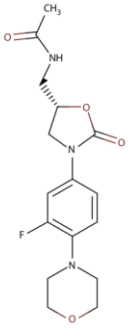


Drug / Drug Class	Recommendation		Certainty in the evidence	Relative (95% CI) Death	Relative (95% CI) Success
	FOR	AGAINST			
Bedaquiline	Strong		Very Low	aOR 0.4 (0.3 to 0.5)	aOR 2.0 (1.4 to 2.9)
Fluoroquinolone: Moxifloxacin	Strong		Very Low	aOR 0.5 (0.4 to 0.6)	aOR 3.8 (2.8 to 5.2)
Fluoroquinolone: Levofloxacin	Strong		Very Low	aOR 0.6 (0.5 to 0.7)	aOR 4.2 (3.3 to 5.4)
Linezolid	Conditional		Very Low	aOR 0.3 (0.2 to 0.3)	aOR 3.4 (2.6 to 4.5)
Clofazimine	Conditional		Very Low	aOR 0.8 (0.6 to 1.0)	aOR 1.5 (1.1 to 2.1)
Cycloserine	Conditional		Very Low	aOR 0.6 (0.5 to 0.6)	aOR 1.5 (1.4 to 1.7)
Injectables: Amikacin	Conditional		Very Low	aOR 1.0 (0.8 to 1.2)	aOR 2.0 (1.5 to 2.6)
Injectables: Streptomycin	Conditional		Very Low	aOR 0.8 (0.6 to 1.1)	aOR 1.5 (1.1 to 2.1)
Ethambutol	Conditional		Very Low	aOR 1.0 (0.9 to 1.2)	aOR 0.9 (0.7 to 1.1)
Pyrazinamide	Conditional		Very Low	aOR 0.7 (0.6 to 0.8)	aOR 0.7 (0.5 to 0.9)
Injectables: Carbapenems w/ clavulanic acid	Conditional		Very Low	aOR 1.0 (0.5 to 1.7)	aOR 4.0 (1.7 to 9.1)
Delamanid	Concur with WHO conditional recommendation				

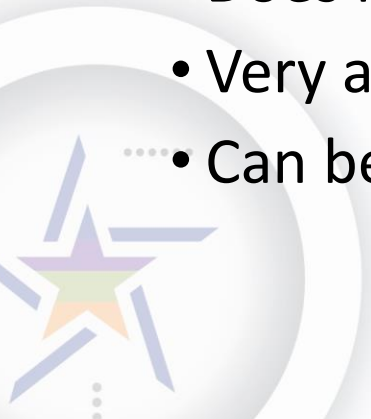
Drug / Drug Class	Recommendation		Certainty in the evidence	Relative (95% CI) Death	Relative (95% CI) Success
	FOR	AGAINST			
Ethionamide Prothionamide		Conditional	Very Low	aOR 0.9 (0.8 to 1.0)	aOR 0.8 (0.7 to 0.9)
Injectables: Kanamycin		Conditional	Very Low	aOR 1.1 (0.9 to 1.2)	aOR 0.5 (0.4 to 0.6)
<i>P</i> -Aminosalicylic Acid		Conditional	Very Low	aOR 1.2 (1.1 to 1.4)	aOR 0.8 (0.7 to 1.0)
Injectables: Capreomycin		Conditional	Very Low	aOR 1.4 (1.1 to 1.7)	aOR 0.8 (0.6 to 1.1)
Macrolides: Azithromycin Clarithromycin		Strong	Very Low	aOR 1.6 (1.2 to 2.0)	aOR 0.6 (0.5 to 0.8)
Amoxicillin- clavulanate		Strong	Very Low	aOR 1.7 (1.3 to 2.1)	aOR 0.6 (0.5 to 0.8)

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

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 co-ad: Serotonergic agents)

Mitochondria Toxicity

Bone marrow suppression - dose dependent/reversible

Peripheral Neuropathy - Not dose dependent (? not reversible):
12-20 weeks of treatment

Optic neuritis: may be rechallenged? (1)

Hyperlactatemia

GI disturbance

Rash



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

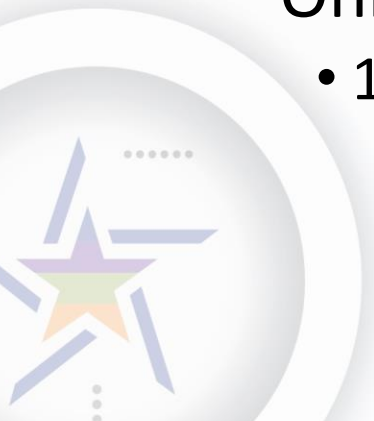
Linezolid for treatment of chronic extensively drug-resistant tuberculosis

- 41 patients with XDR-TB unresponsive to therapy in the previous 6 months
- Linezolid 600 mg/day initially then after 4 months or sputum smear conversion either 600 mg/day or 300 mg/day
- 87% with neg sputum cultures at 6 mos
 - 13 completed therapy without relapse
- Acquired linezolid resistance in 4 (3 who received 300 mg/day)



Linezolid for treatment of chronic extensively drug-resistant tuberculosis

- **82% clinically significant adverse events (AE's)** possibly or probably linezolid related
 - 7 episodes of myelosuppression (anemia and leukopenia)
 - 7 episodes optic neuropathy
 - 21 episodes of peripheral neuropathy
 - 1 episode rhabdomyolysis
- Only 3 patients permanently discontinued linezolid owing to drug toxicity
 - 1 anemia, **2 optic neuropathy**



Bedaquiline

- 2012 Bedaquiline FDA approved for treatment of drug resistant TB
 - CDC oversight of all prescription requests
- 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

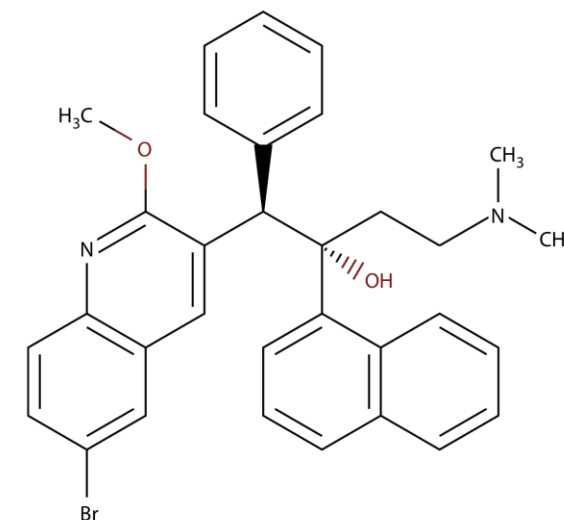


TABLE 1. Pharmacokinetic (PK) parameters of bedaquiline in healthy volunteers, by selected characteristics

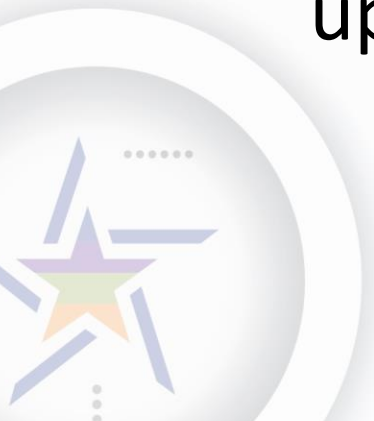
PK characteristic	PK parameter	
Dose-proportionality	PK dose-proportional for doses 10–700 mg	
Absorption	T _{max} (median)	~5 hrs
	t _{1/2} term	~4–5 mos
	Food effect	High-fat meal increased peak plasma concentration (C _{max}) and plasma exposure by twofold
Distribution	Protein binding	>99%
Metabolism	Pathways	Metabolized to M2 and M3 by CYP3A4

Source: Adapted from Food and Drug Administration clinical pharmacology review (9).

Abbreviations: M = metabolite; CYP = cytochrome P450; t_{1/2} term = mean terminal half-life; T_{max} = time of maximum serum level.

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*)



Bedaquiline

- Adding bedaquiline to optimized MDR-TB and XDR-TB background regimens results in
 - Faster culture conversion: 79% vs. 58% in 24 weeks
 - Increased early bactericidal activity
 - High rates of culture conversion 62% vs. 44% in 120 weeks



- 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 have been substantiated by several studies
- Dose adjustment is not required in case of mild-to-moderate renal impairment

TABLE 5. Mortality in bedaquiline Phase II safety studies*

Study (Stage)	Design	No. of deaths			
		Bedaquiline arm		Control arm	
		No.	(%)	No.	(%)
C202	Randomized, open-label, dose-ranging early bactericidal study using INH or RIF in control arm	2/45	(4.4)	0	0
C208 (Stage 1)	Double-blind, randomized, placebo-controlled superiority trial	2/23	(8.7)	2/124	(8.3)
C208 (Stage 2)	Double-blind, randomized, placebo-controlled superiority trial	10/79	(12.6)	4/81	(4.9)
C209	Noncomparative, single-arm, open-label trial	16/233	(6.9)	No control arm	No control arm

Source: Adapted from Food and Drug Administration clinical pharmacology review (9).

Abbreviations: INH = isoniazid; RIF = rifampin.

* Patients in the mortality analysis were followed for up to 6 months from the last recorded visit, as specified in the study safety procedures.

Bedaquiline: Side Effects

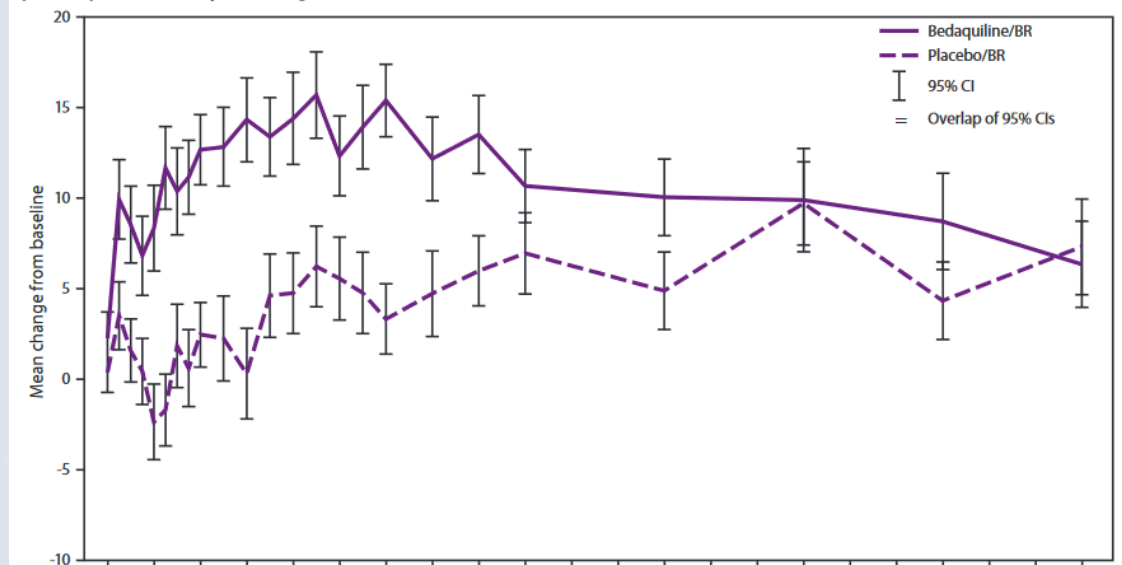
- Nausea (35%)

First two weeks, usually they develop GI symptoms, but better after cut down the medications.

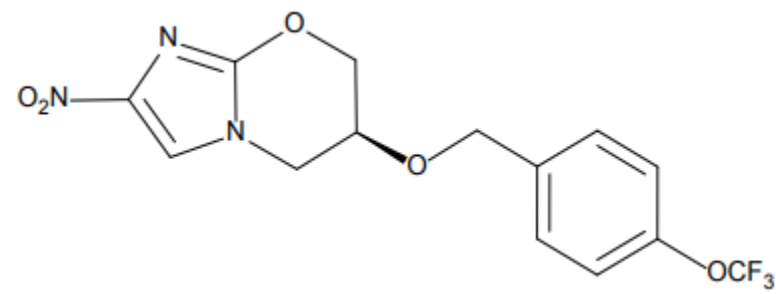
- QT prolongation: 9% increased > 60ms
- ECG should be obtained before initiation, & at least 2, 12 & 24 weeks after starting treatment.

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

FIGURE 2. Mean changes from baseline in QTcF* over time among patients treated with bedaquiline plus background regimen[†] (BR) versus placebo plus BR — Study C208 (Stage 2)



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)

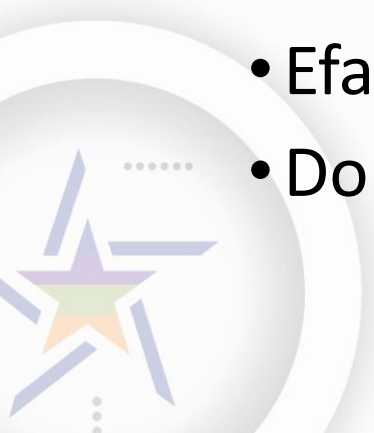


Pretomanid

- 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 (BP_aL) for pulmonary XDR/MDR Tb in the U.S.

D-D Interaction

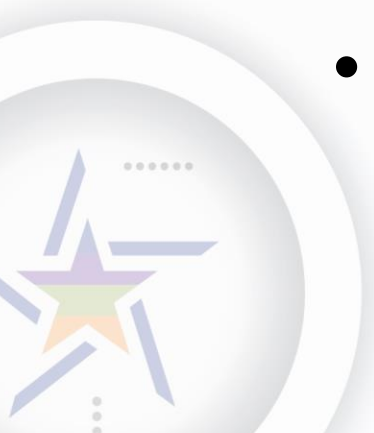
- Efavirenz reduces pretomanid exposure
- Dolutegravir based: No interaction



Pretomanid: Potential Side Effects

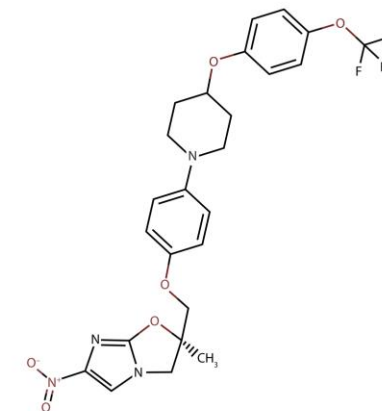
Data from BPaL (Nix-TB trial)

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



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 (1)

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

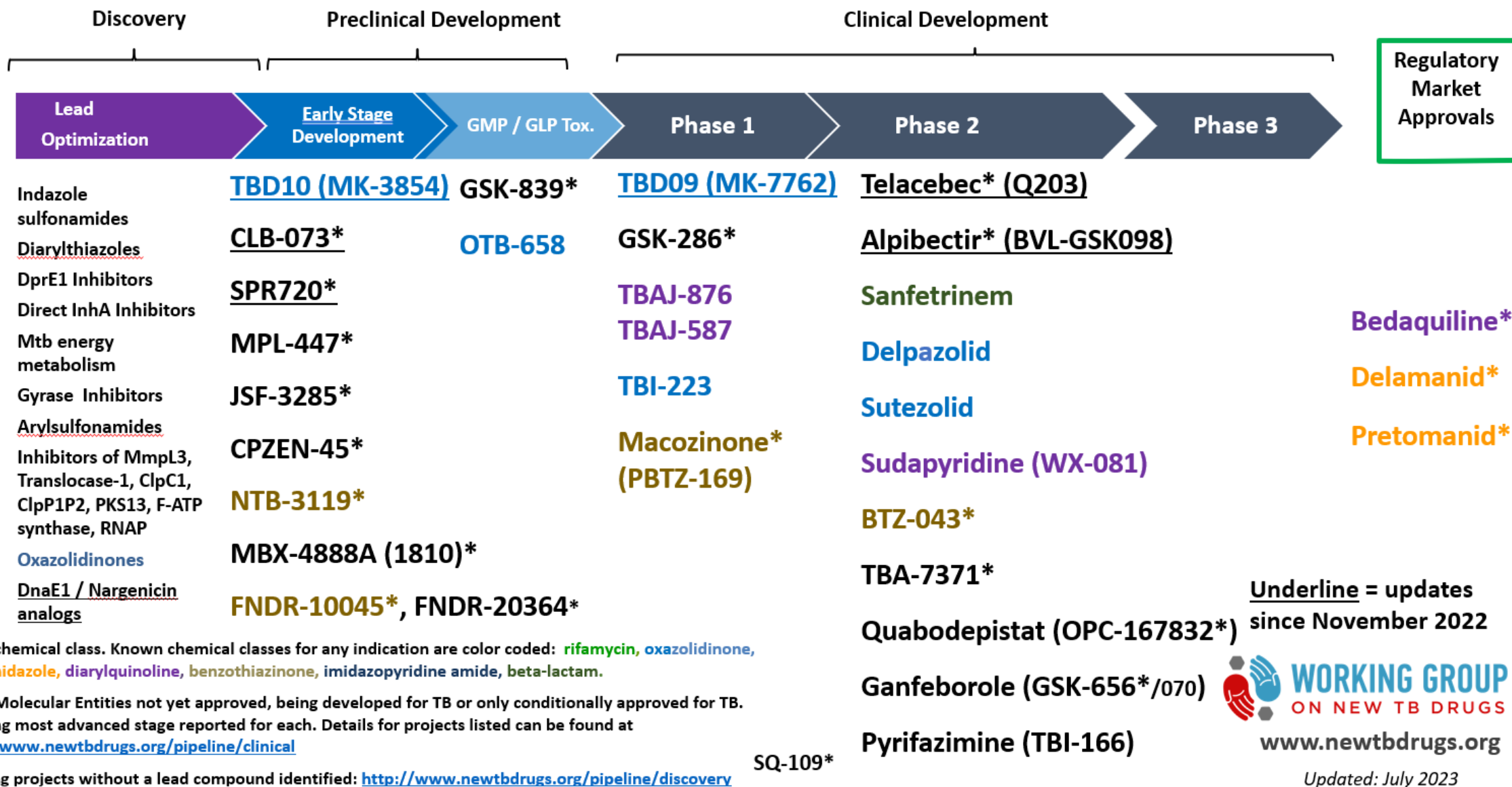
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QT interval prolongation

- 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



2023 Global New TB Drug Pipeline¹ Updated 7/14/2023



Conclusion

- Thank you for listening and to Dr. Nigo for letting us utilize your slides and Dr. Armitige for the updates!



Questions?

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Or

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