Tuberculosis Drugs

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July 16, 2024

TB Intensive
July 16 – 18, 2024
San Antonio, Texas

Tuberculosis Drugs
First line Drugs

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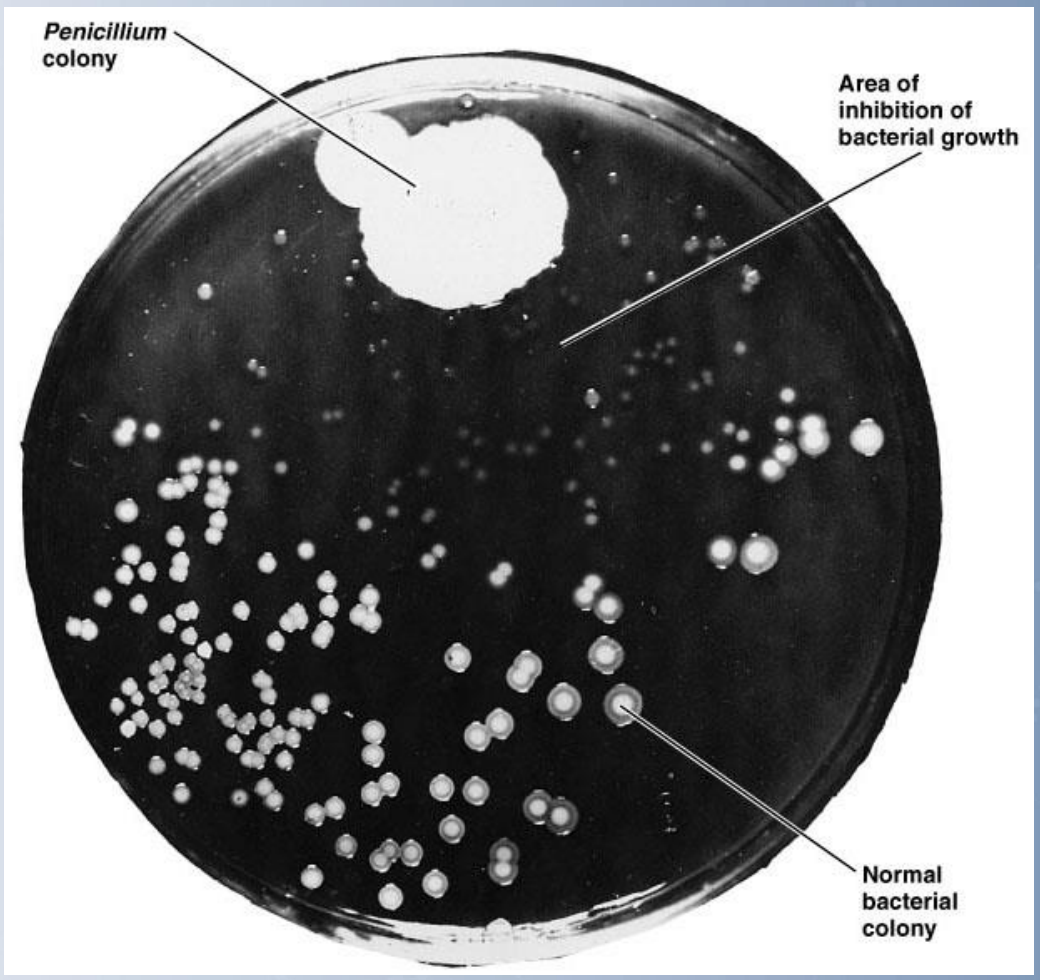
Lisa Armitige, MD, PhD has the following disclosures to make:

- Consultant for Oak Therapeutics

Objectives

- Discuss the mechanism of action and efficacy of each first line TB medication; rifampin, INH, ethambutol and PZA
- Discuss fluoroquinolone in treatment of tuberculosis
- Discuss toxicity associated with each drug

- **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 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

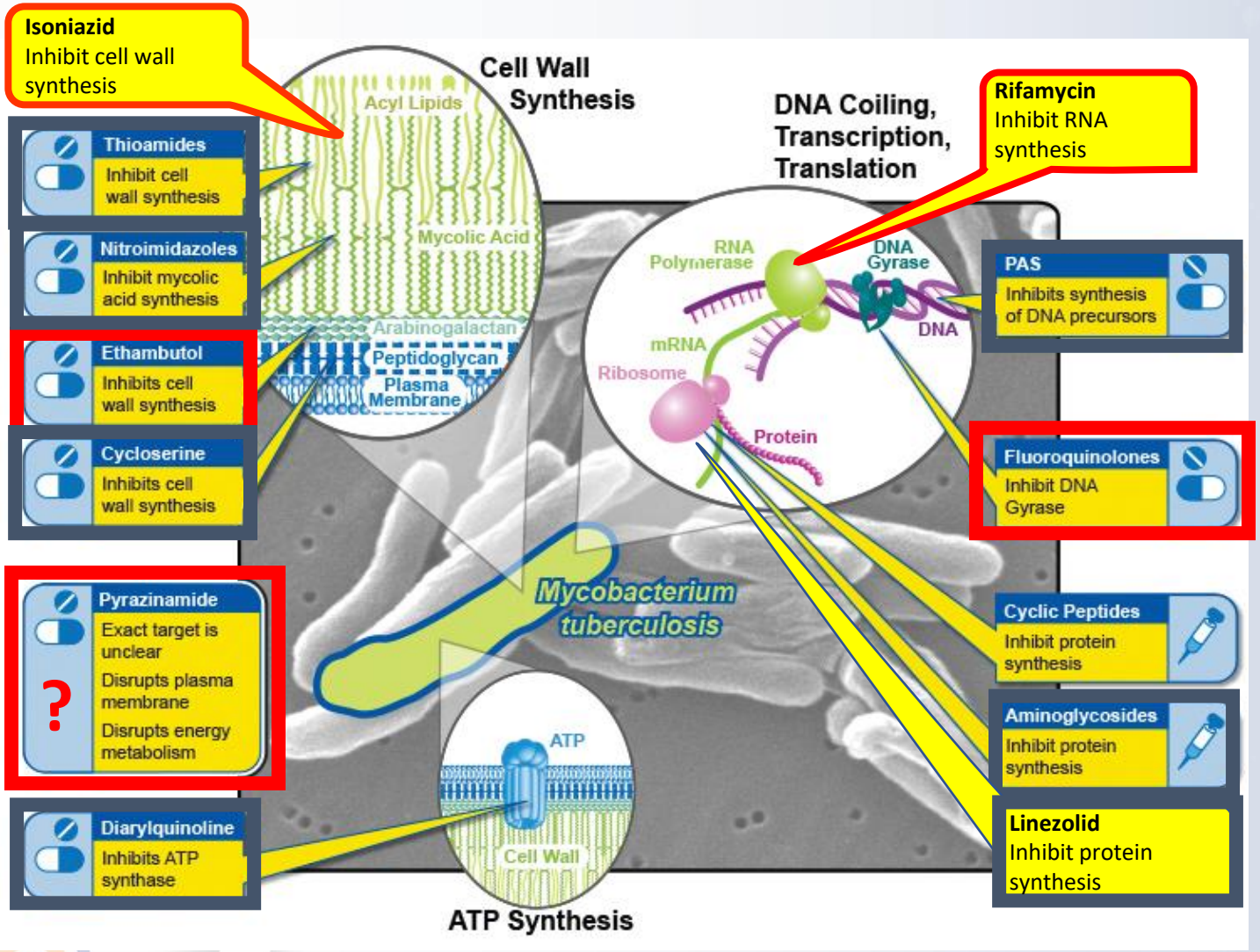
Clinical Tuberculosis 5th Edition 2014

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.

Mechanism of Action: Current Mtb meds



Thioamides: Ethionamide

Diarylquinoline: Bedaquiline

Nitroimidazoles: Delamanid

Modified Figure
https://www.niaid.nih.gov/diseases-conditions/tbdrugs
Accessed on 8/17/2023

Isoniazid (INH)

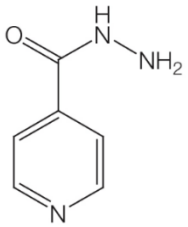


Figure 123.1. Chemical structure of isoniazid (isonicotinic acid hydrazide).

- 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.

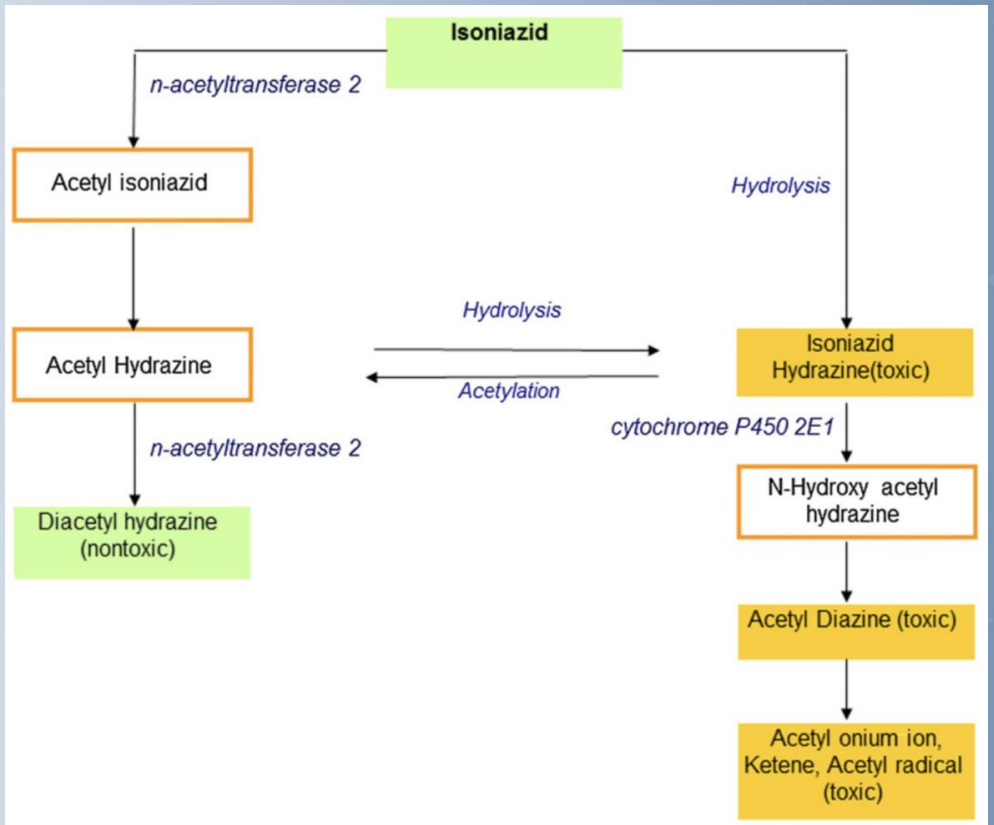


Figure 1 Pathways involved in the metabolism of isoniazid.

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

INH Peripheral Neurotoxicity

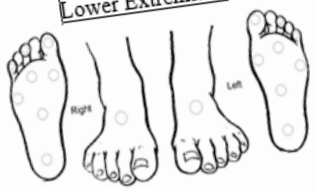
- Dose Related, Functional vitamin B6 deficiency (blocking conversion of B6 to pyridoxal phosphate/enhance excretion (1))
- Uncommon (< 0.2%) at conventional doses
  - Increased risk for neuropathy: Diabetic, alcoholic, HIV infection, pregnancy, poor nutrition, hypothyroidism
- Retrobulbar (optic) neuritis: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

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

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

Peripheral Neuropathy Evaluation

Lower Extremities



Upper 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?

	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:

8 Hypoesthesia to tou
9 Hypoesthesia to pri
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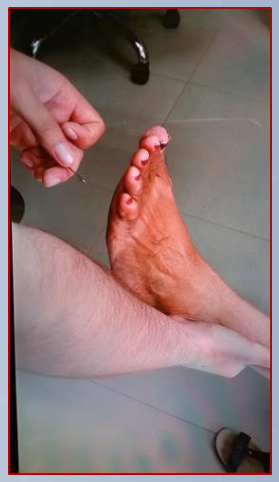
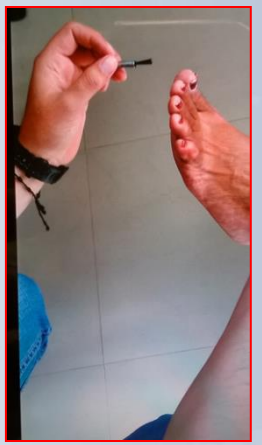





MONITOR ALL THE DANGER SIGNS.
There...do you feel that?
©2007 Diabetes Health

RIFAMPIN (RIF)

(Rifamycins: rifampin, rifabutin, rifapentine)

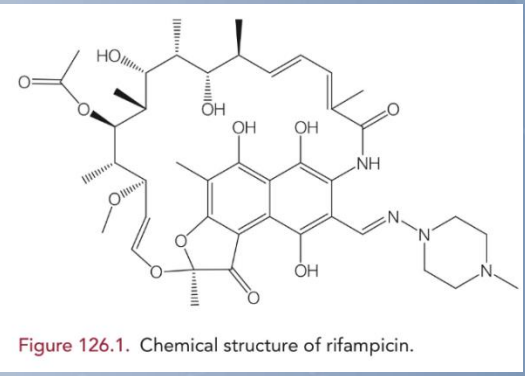


Figure 126.1. Chemical structure of rifampicin.

- 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

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

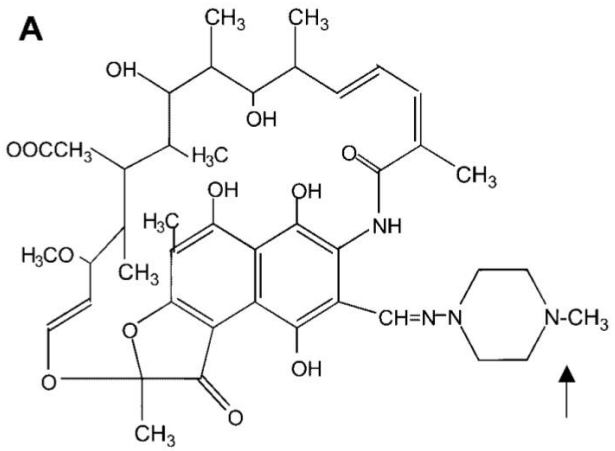
- CDC recommends **3HP for latent TB**.
- Long acting rifamycin is highly protein bound that can be used once weekly with INH for latent TB therapy.
- Interim CDC guidance: A part of **4 month regimen** for active Tb. (1)
- Adverse effects similar to rifampin

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

<u>Pill Burden & Price</u>

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

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



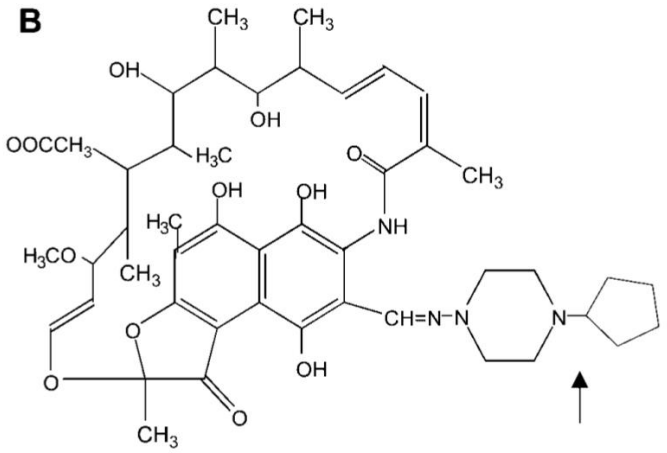


Table 1. Comparing features of rifampin versus rifapentine.

	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.

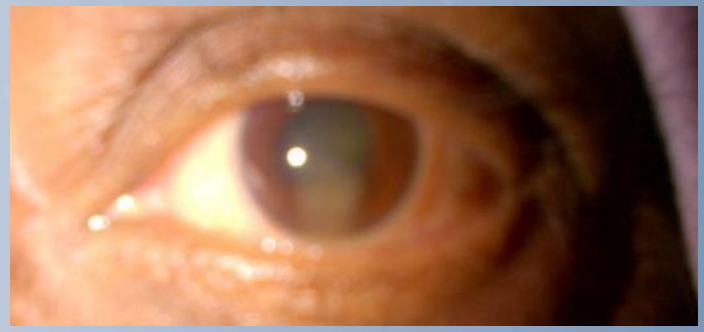
- **Less severe induction of hepatic microsomal enzymes than rifampin**, therefore, less effect on the metabolism of other drugs

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

(1) IDSA 2016 guideline

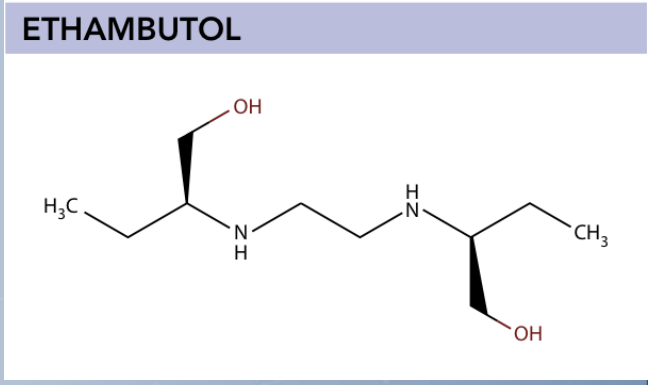
Rifabutin Toxicity

- 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 (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.

(1) IDSA 2016 guideline

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.

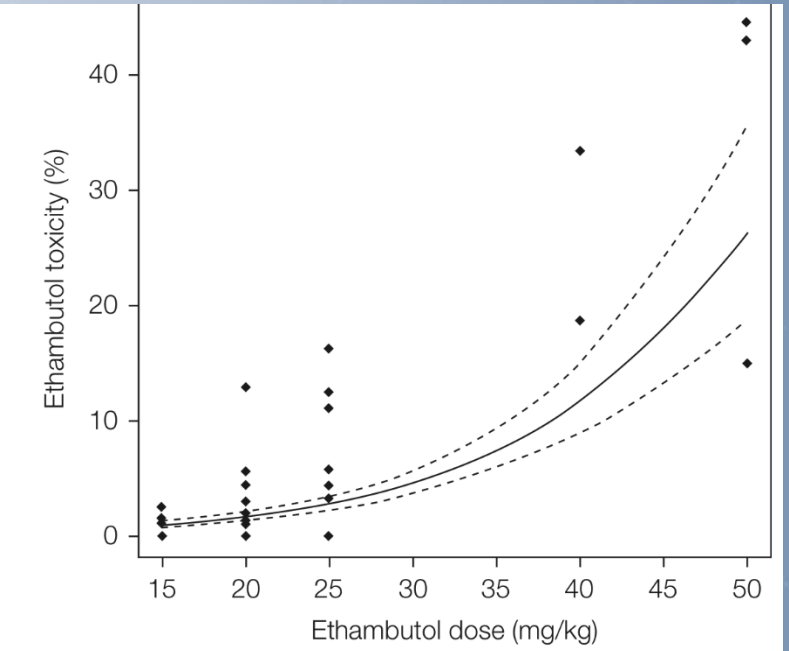


Figure 124.2. Ocular toxicity and dose of ethambutol. $y = \exp(-6.0599 + 0.l006*\text{dose})/(l + \exp(-6.0599 + 0.l006*\text{dose}))$. The broken lines represent the 95% confidence interval limits. (From WHO, 2006.)

Kucers' The Use of Antibiotics 7th

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

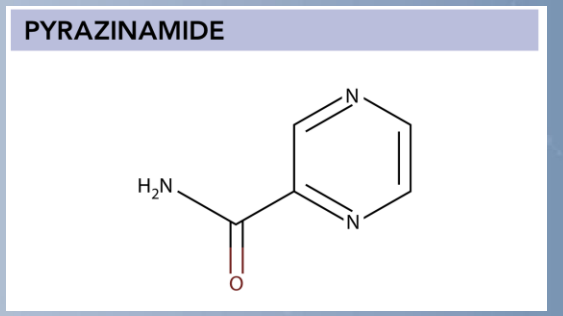
Management

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

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

- Refer to ophthalmology

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

Kucers' The Use of Antibiotics 7th

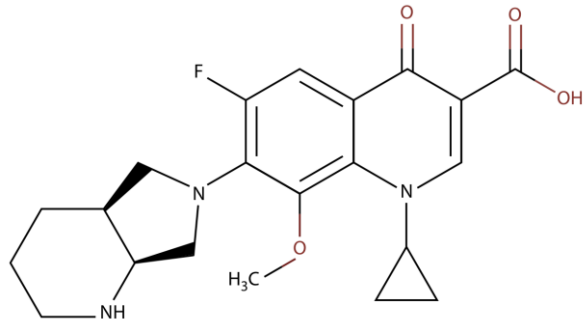
Fluoroquinolones

- Inhibit DNA gyrase and Topoisomerase IV
- Levofloxacin and Moxifloxacin

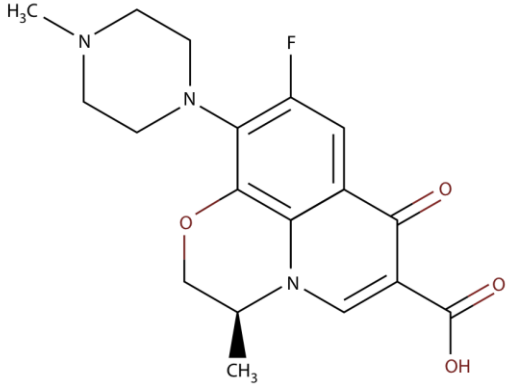
- Oral bioavailability > 90%
- MFX: 400mg daily, and up to 800mg
- LFX: 750mg daily up to 1000mg

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



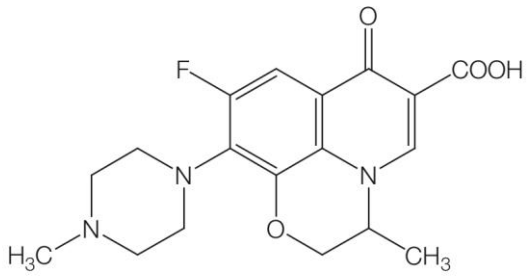


Figure 103.1. Chemical structure of ofloxacin.

Adverse Effects of FQN

Gastrointestinal disturbance: nausea/bloating 0.5-2%

QTc Prolongation

- MFX: 6.4 - 14.9 ms at Cmax
- LFX: 6ms

Tendinopathy

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

CNS toxicity

- Psychiatric disturbance/lower seizure threshold

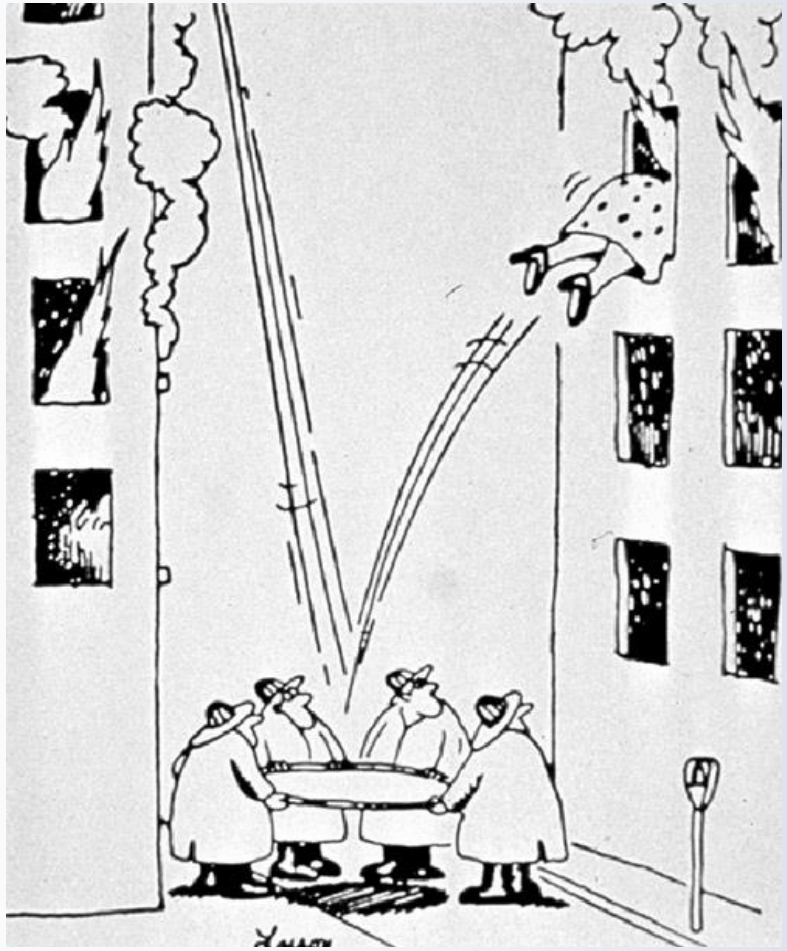
Fluoroquinolone Toxicity Musculoskeletal

- 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	

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):

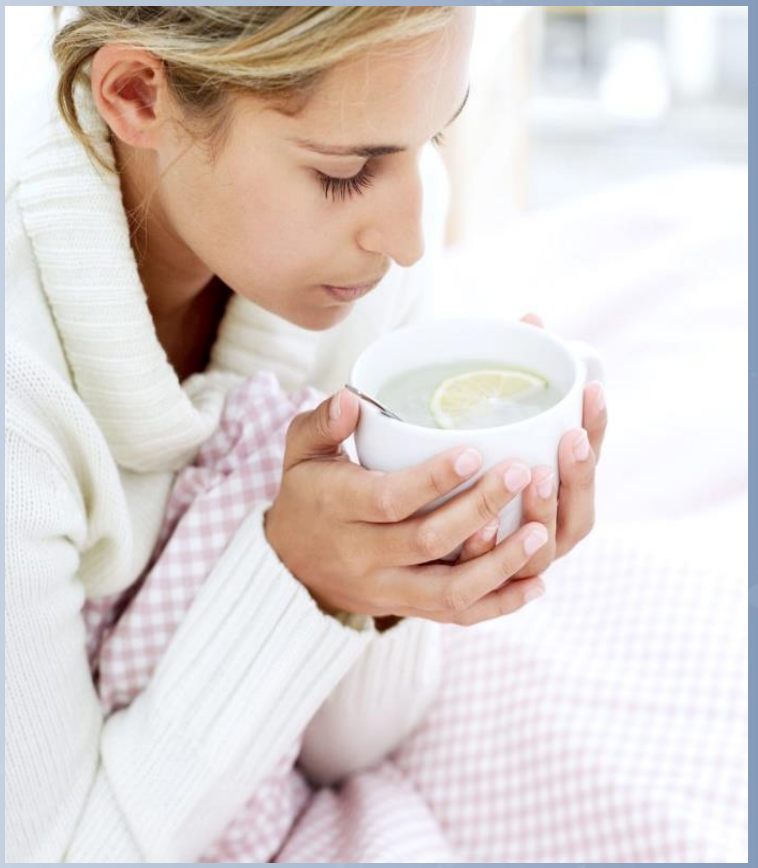
Gastrointestinal Upset

- 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

<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.
- Bili/INR/APTT

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

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: may elect not to 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)

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.

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)

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

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

IDSA Guideline 2016

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.

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

Interact with anticonvulsant, like phenytoin

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

Tuberculosis Drugs
Second line Drugs

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Objectives

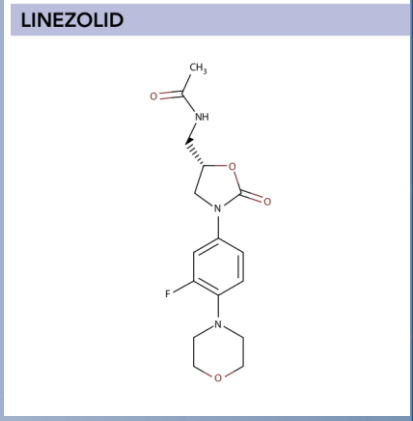
- Discuss the mechanism of action and efficacy of each 2nd line drugs
- Discuss toxicity associated with each drug

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)
P-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)

Myungsun et al NEJM 2012, 367; 1508

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**

Myungsun et al NEJM 2012, 367; 1508

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

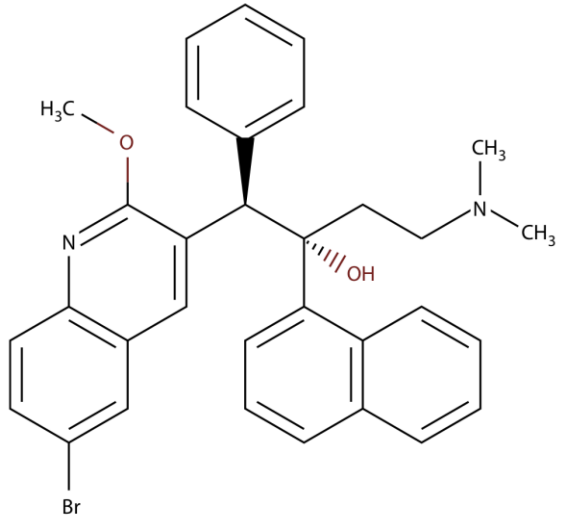


TABLE 1. Pharmacokinetic (PK) parameters of bedaquiline in healthy volunteers, by selected characteristics

PK characteristic	PK parameter	
Dose-proportionality	PK dose-proportional for doses 10–700 mg	
Absorption	Tmax (median)	~5 hrs
	t½ term	~4–5 mos
	Food effect	High-fat meal increased peak plasma concentration (Cmax) 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; t½ term = mean terminal half-life; Tmax = 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


ORIGINAL ARTICLE

Multidrug-Resistant Tuberculosis and Culture Conversion with 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 No.	Bedaquiline arm (%)	Control arm No.	Control arm (%)
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.

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

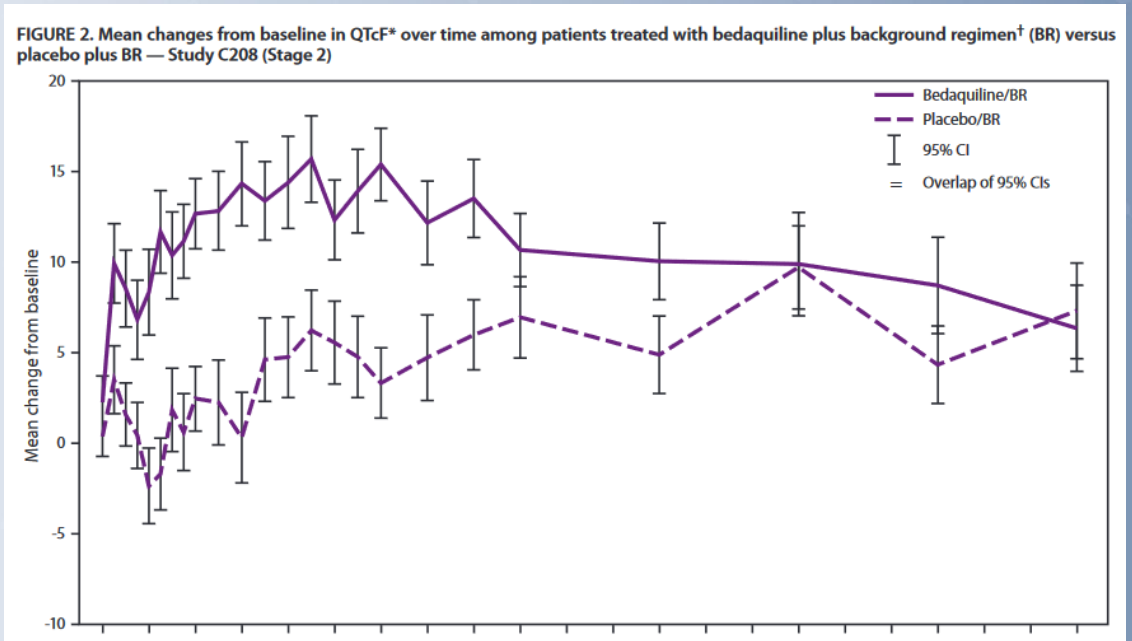
Bedaquiline: Side Effects

- Nausea (35%)

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

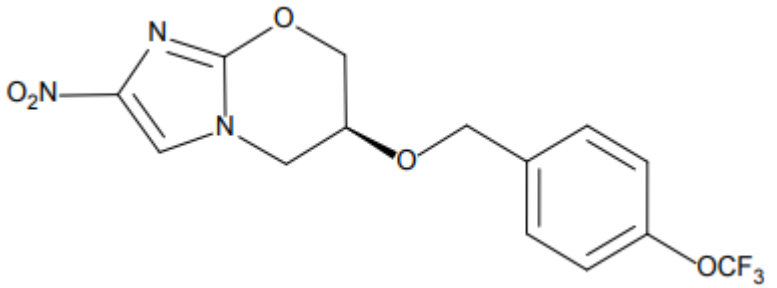
- QT prolongation: 9% increased > 60ms
- ECG should be obtained before initiation, & at least 2, 12 & 24 weeks after starting treatment.

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



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.

D-D Interaction

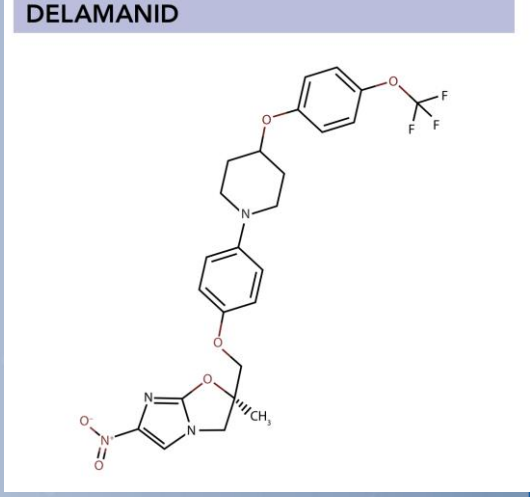
- Efavirenz reduces pretomanid exposure
- Dolutegravir based: No interaction

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

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

2023 Global New TB Drug Pipeline[1] Updated 7/14/2023

Discovery | Preclinical Development | Clinical Development

Lead Optimization → Early Stage Development → GMP / GLP Tox. → Phase 1 → Phase 2 → Phase 3 → Regulatory Market Approvals

Indazole sulfonamides
Diarylthiazoles
DprE1 Inhibitors
Direct InhA Inhibitors
Mtb energy metabolism
Gyrase Inhibitors
Arylsulfonamides
Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP
Oxazolidinones
DnaE1 / Nargenicin analogs

TBD10 (MK-3854)
CLB-073*
SPR720*
MPL-447*
JSF-3285*
CPZEN-45*
NTB-3119*
MBX-4888A (1810)*
FNDR-10045*, FNDR-20364*

GSK-839*
OTB-658

TBD09 (MK-7762)
GSK-286*
TBAJ-876
TBAJ-587
TBI-223
Macozinone* (PBTZ-169)

Telacebec* (Q203)
Alpibectir* (BVL-GSK098)
Sanfetrinem
Delpazolid
Sutezolid
Sudapyridine (WX-081)
BTZ-043*
TBA-7371*
Quabodepistat (OPC-167832*)
Ganfeborole (GSK-656*/070)
Pyrifazimine (TBI-166)

SQ-109*

Bedaquiline*
Delamanid*
Pretomanid*

Underline = updates since November 2022

*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: July 2023

https://docs.google.com/presentation/d/0B3BR7L--n_1AQ0c1ZjY5bzF3VnM/edit?resourcekey=0-2_9AtXD5aeK9t_lpHwllcA#slide=id.p1

- Thank you for listening!

  (and, thank you, Dr. Nigo for the use of your slides)

Questions?

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Or

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