TB Drugs

Masayuki Nigo, MD, MSc

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TB Intensive
September 13 – 15, 2023
Richmond, TX

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Masayuki Nigo, MD, MSc has the following disclosures to make:

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

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Tuberculosis Drugs
First line Drugs

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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

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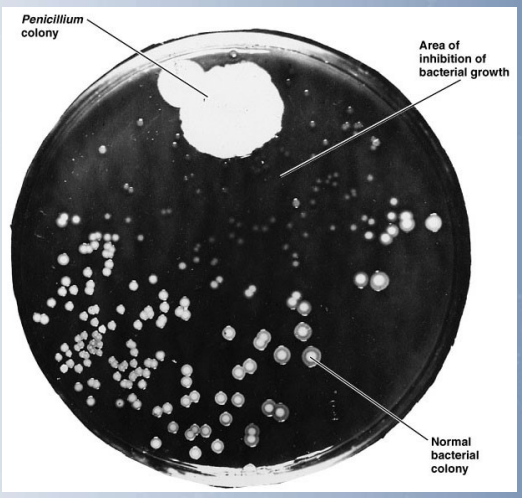
- **1928** – Fleming discovered penicillin, produced by *Penicillium*.
- **1940** – Howard Florey and Ernst Chain performed first clinical trials of penicillin.
- **1943** -Albert Schatz (Selman Waksman, 1952 Nobel) discovered **streptomycin**
- **1951** – **Isoniazid** discovered
- **1952** – **Pyrazinamide**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



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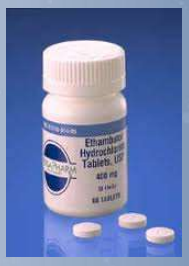
ANTITUBERCULOSIS DRUGS

- 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
  - Delamanid*



IDSA Guideline 2016

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Why need four drugs?

- Mtb produces the drug-resistant mutants during the 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

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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.

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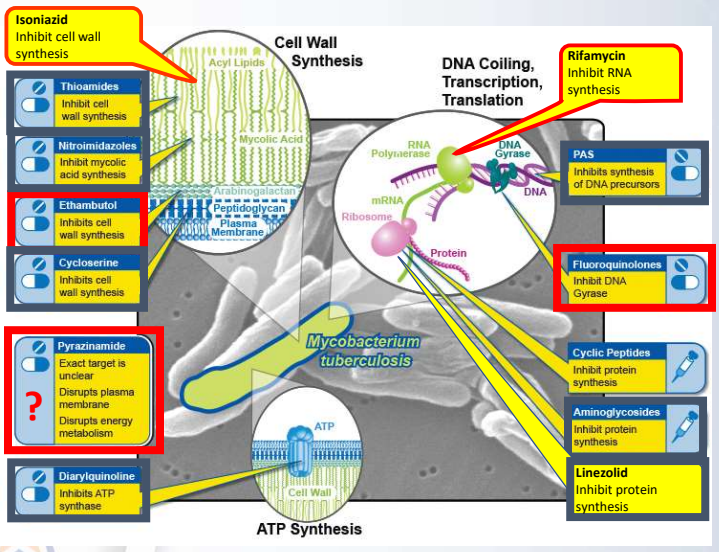
Mechanism of Action: Current Mtb meds



Thioamides: Ethionamide
Diarylquinoline: Bedaquiline
Nitroimidazoles: Delamanid

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

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Isoniazid (INH)

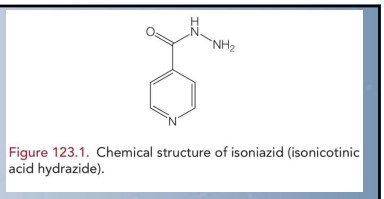

Figure 123.1. Chemical structure of isoniazid (isonicotinic acid hydrazide).

- Inhibits mycolic acid synthesis
- INH is a prodrug that 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: 5mg/kg (300 mg/daily), 20-30 mg/kg (900 mg) twice or three times weekly

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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.

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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.

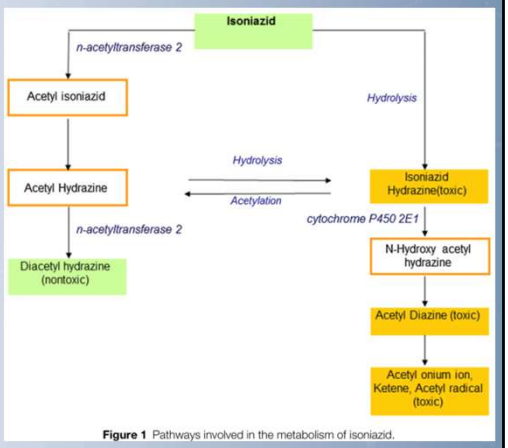

Figure 1 Pathways involved in the metabolism of isoniazid.

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

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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

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Peripheral Neuropathy Evaluation
Lower Extremities
Upper Extremities
PATIENT'S INTERVIEW (Ask your patient the following questions:
Question 1:
Yes
No
Question 2: Does your pain have any of these characteristics?
1 Burning
2 Freezing pain?
3 Electric shock-type sensation?
Question 3: Do you have any of these symptoms in the area?
4 Tingling
5 Prickling
6 Numbness
7 Stinging/Itching
Question 4: Is the pain made worse with the touch of clothing or bed sheets?
PATIENT'S ASSESSMENT
Question 5:
8 Hypoesthesia to touch
9 Hypoesthesia to prick
10 Extreme sensitivity to touch
11 Extreme sensitivity to prick

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

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RIFAMPIN (RIF)

(Rifamycins: rifampin, rifabutin, rifapentine)

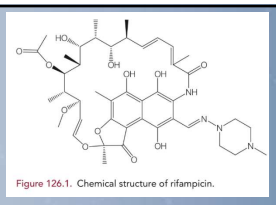

Figure 126.1. Chemical structure of rifampicin.

- 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

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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

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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)

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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

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

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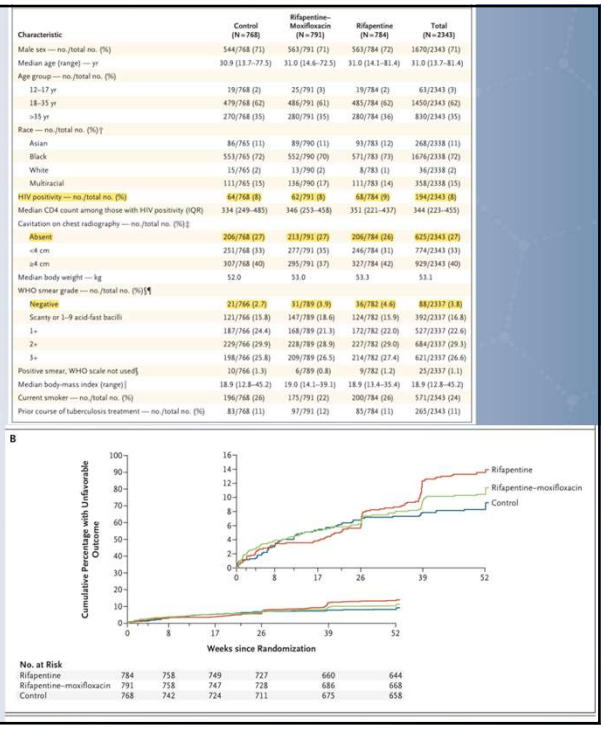
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium



Characteristic	Control (N=768)	Rifapentine–Moxifloxacin (N=791)	Rifapentine (N=784)	Total (N=2343)
Male sex — no./total no. (%)	544/768 (71)	563/791 (71)	563/784 (72)	1670/2343 (71)
Median age (range) — yr	30.9 (13.7–77.5)	31.0 (14.6–72.5)	31.0 (14.1–81.4)	31.0 (13.7–81.4)
Age group — no./total no. (%)				
12–17 yr	19/768 (2)	25/791 (3)	19/784 (2)	63/2343 (3)
18–35 yr	479/768 (62)	486/791 (61)	485/784 (62)	1450/2343 (62)
>35 yr	270/768 (35)	280/791 (35)	280/784 (36)	830/2343 (35)
Race — no./total no. (%)†				
Asian	86/765 (11)	89/790 (11)	93/783 (12)	268/2338 (11)
Black	553/765 (72)	552/790 (70)	571/783 (73)	1676/2338 (72)
White	15/765 (2)	13/790 (2)	8/783 (1)	36/2338 (2)
Multiracial	111/765 (15)	136/790 (17)	111/783 (14)	358/2338 (15)
HIV positivity — no./total no. (%)	64/768 (8)	62/791 (8)	68/784 (9)	194/2343 (8)
Median CD4 count among those with HIV positivity (IQR)	334 (249–485)	346 (253–458)	351 (221–437)	344 (223–455)
Cavitation on chest radiography — no./total no. (%)‡				
Absent	206/768 (27)	213/791 (27)	206/784 (26)	625/2343 (27)
<4 cm	251/768 (33)	277/791 (35)	246/784 (31)	774/2343 (33)
≥4 cm	307/768 (40)	295/791 (37)	327/784 (42)	929/2343 (40)
Median body weight — kg	52.0	53.0	53.3	53.1
WHO smear grade — no./total no. (%)¶				
Negative	21/766 (2.7)	31/789 (3.9)	36/782 (4.6)	88/2337 (3.8)
Scanty or 1–9 acid-fast bacilli	121/766 (15.8)	147/789 (18.6)	124/782 (15.9)	392/2337 (16.8)
1+	187/766 (24.4)	168/789 (21.3)	172/782 (22.0)	527/2337 (22.6)
2+	229/766 (29.9)	228/789 (28.9)	227/782 (29.0)	684/2337 (29.3)
3+	198/766 (25.8)	209/789 (26.5)	214/782 (27.4)	621/2337 (26.6)
Positive smear, WHO scale not used‖	10/766 (1.3)	6/789 (0.8)	9/782 (1.2)	25/2337 (1.1)
Median body-mass index (range)‖	18.9 (12.8–45.2)	19.0 (14.1–39.1)	18.9 (13.4–35.4)	18.9 (12.8–45.2)
Current smoker — no./total no. (%)	196/768 (26)	175/791 (22)	200/784 (26)	571/2343 (24)
Prior course of tuberculosis treatment — no./total no. (%)	83/768 (11)	97/791 (12)	85/784 (11)	265/2343 (11)

- Three arms
1. INH, RIF, EB, PZA (2), INH, RIF (4)
2. INH, **RIP**, EB, PZA (2), INH, **RIP** (2)
3. INH, **RIP**, **MOX**, PZA (2), INH, RIP, **MOX** (2)

Cardiac event: 3 (0.4%) in RIP/MOX

Only 1 related to QT Prolongation

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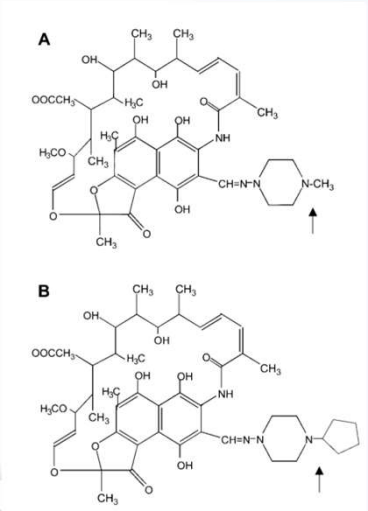

Table 1. Comparing features of rifampin versus rifapentine.

	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.

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Rifabutin

- A substitute for rifampin for patients who are receiving drugs, especially antiretroviral drugs, that have unacceptable interactions with rifampin.
- Adverse effects: Less severe induction of hepatic microsomal enzymes, therefore, less effect on the metabolism of other drugs
- Adult dose 5 mg/kg (300 mg daily).

(1) IDSA 2016 guideline

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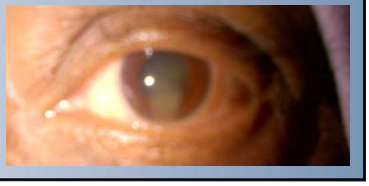
Rifabutin Toxicity

- 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

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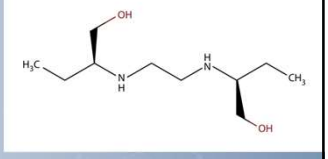
Ethambutol (EMB)

ETHAMBUTOL



- 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

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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

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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.

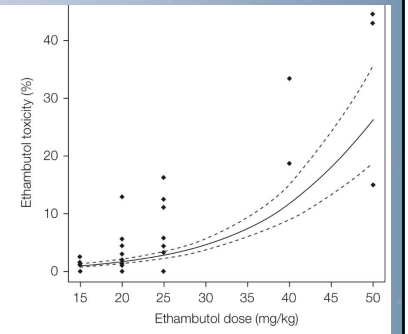

Figure 124.2. Ocular toxicity and dose of ethambutol. $y = \exp(-6.0599 + 0.1006*\text{dose})/(1 + \exp(-6.0599 + 0.1006*\text{dose}))$. The broken lines represent the 95% confidence interval limits. (From WHO, 2006.)

Kucers' The Use of Antibiotics 7th

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EMB Toxicity: Monitoring

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

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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

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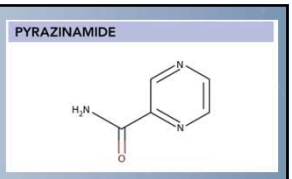
Pyrazinamide (PZA)



- 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.

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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

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PZA Gout Attack

- Colchicine should be avoided
  - Levels are unpredictable (increased by INH but decreased by RIF)
- NSAIDS/steroids are safe to give during Mtb Treatment.

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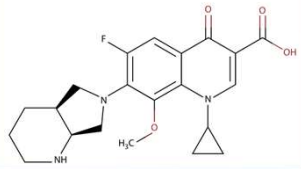
Fluoroquinolones

- Inhibit DNA gyrase and Topoisomerase IV
- Levofloxacin and Moxifloxacin

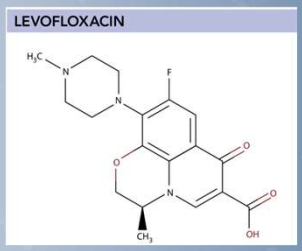
- Oral bioavailability > 90%
- MFX: 400mg daily, and up to 800mg
- LFX: 750mg daily up to 1000mg

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



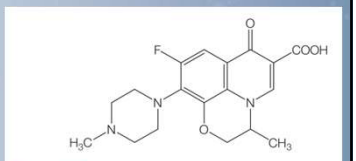


Figure 103.1. Chemical structure of ofloxacin.

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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

Clinical Tuberculosis 6th Edition

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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

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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	

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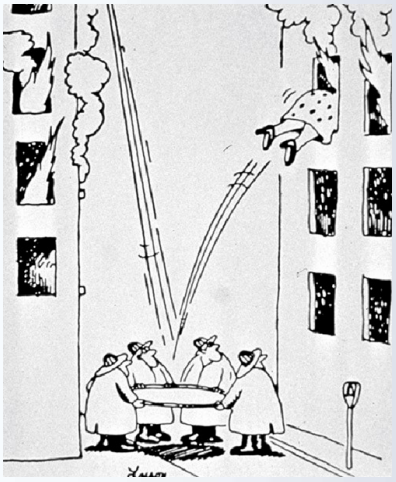
Common Adverse Effects



Sometimes our interventions can be dangerous…

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TB Disease: Baseline Testing and Monitoring

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

IDSA guideline 2016

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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):

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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

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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 except EMB and add FQN. Rechallenge one by one. (Consultation)

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Hepatotoxicity of TB Drugs
Drug Induced Liver Injury (DILI)

- **Hepatotoxic**
  - **INH**
  - **Rifampin/Rifabutin**
  - **PZA**
  - Ethionamide
  - PAS
  - (Fluoroquinolones)

- Non-hepatotoxic ("Liver friendly")
  - **Ethambutol**
  - Cycloserine
  - Strep/Amikacin
  - Capreomycin
  - (Fluoroquinolones)

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Risk Factors for Hepatotoxicity

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

Monitoring Hepatotoxicity

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

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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)

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Interventions for Hepatotoxicity (PZA sparing: Common Scenario)

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

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

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

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

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Rifabutin

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

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

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Rash

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

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- **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

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Tb drugs and renal diseases

- Decreasing the dose of selected Mtb drugs may not be the best method of treating tuberculosis
- The peak serum concentrations may be too low. Increasing the dosing interval is recommended.

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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.)

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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.

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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

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Common Rifampin Drug Interactions

IMPOSSIBLE TO REMEMBER ALL
Remember potential life threatening int.

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

Useful Websites

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

HIV meds

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

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Tuberculosis Drugs
Second line Drugs

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9/13/23

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Masayuki Nigo has the following disclosures to make:

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

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Objectives

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

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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

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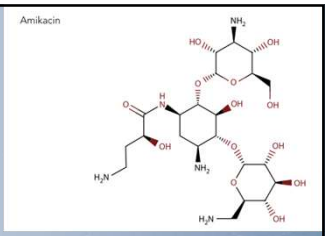
Amikacin "Injectable drugs"



- Bind to 16S ribosomal subunit
- Baseline and monthly serum creatinine
- 15mg/kg IV or IM q24hr (Adjusted Body Weight)
- If CrCL < 70ml/min., consider use of intermittent dosing initially (2-3 times a week)

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Therapeutic drug monitoring

- Monitor serum drug levels and adjust dose accordingly
- Once daily dosing is preferred.
  1) Cmax
  2) Post Antibiotic Effect
  3) Low trough

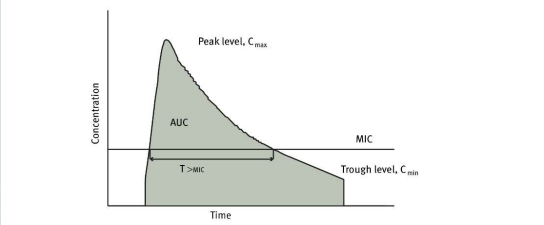

Figure 1 AUC, area under the concentration-time curve: C_{min}, minimum concentration: C_{max}, maximum concentration: MIC minimum inhibitory concentration: T>MIC, time during which the drug blood concentration is above the MIC [1]

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

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Amikacin: Side Effects

- **Ototoxicity**: hearing disturbances, less vestibular dysfunction than Streptomycin
  Total Cumulative Dosage rather Cmax
  Baseline audiogram (*High Freq. 6,000-8,000 Hz*) & vestibular testing
  Repeat audiogram or vestibular testing if symptoms develop

- **Nephrotoxicity**: 3.4-8.7% of patients, increased risk with pre-existing renal disease, higher doses, other nephrotoxic drugs
- Rash
- Electrolyte disturbances: hypokalemia, hypomagnesemia (Cardiac dysrhythmias)

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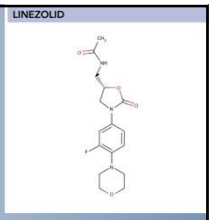
Linezolid: Oxazolidinone



- 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 (Optimal dose unknown)

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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

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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

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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

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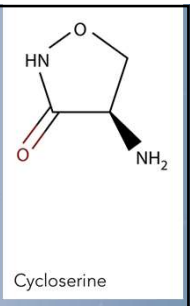
Cycloserine



Cycloserine

- Block peptidoglycan synthesis: Block cell synthesis
- Bacteriostatic agent

- 10-15mg/kg orally in 2 divided doses (Max 500mg BID)
- Pyridoxine may reduce CNS toxicity

  Drug levels are necessary

  (peak levels 20-35 mcg/ml)

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Cycloserine

- Rapid, good GI absorption (65-90%)
- Widely distributed in most body fluids and tissues including **CSF** (80%-100% of plasma) and breast milk

- Excretion is primarily renal, half-life is longer in renally impaired patients (serum levels required with renal insufficiency)
- Not recommended for patients with ESRD

Clinical Tuberculosis 6th Edition

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Cycloserine: Side Effects

- **Central Nervous System Effects:** headaches, restlessness, suicidal ideation psychosis, seizures. May exacerbate underlying seizure disorders or mental illness.
- Administer with caution to alcoholics, patients with hx of mental illness or seizures
- Peripheral neuropathy
- Rash: Photosensitivity

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Clofazimine For Mycobacterial Disease

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

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

Cross resistance with bedaquiline (may not help prevent resistance)

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

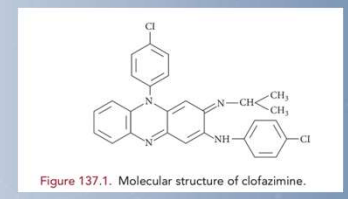
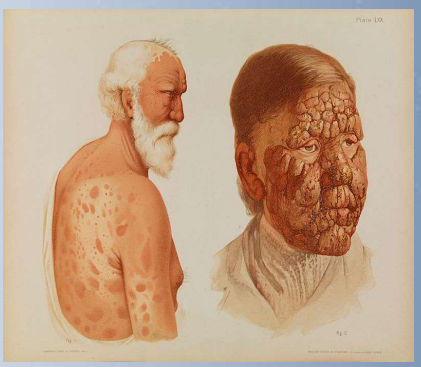


Figure 137.1. Molecular structure of clofazimine.



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Clofazimine for the Treatment of MDR-TB: Prospective, Multicenter, Randomized Controlled Study in China

- 105 patient with MDR-TB randomized to individual based chemotherapy ± clofazimine 100 mg/day for 21 months
- In the clofazimine group:
  - Sputum culture conversion
  - Cavity closure earlier
  - treatment success rate higher 74% vs 54%, p=0.47
  - no difference in discontinuation of therapy (skin discoloration nearly universal with clofazamine)

Tang et al 2015. CID; 60: 1361

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Clofazimine: Side Effects

Common

- **Skin discoloration**
- Skin rash and itching

GI Side Effects (40-50%)

- Diarrhea
- Loss of appetite
- Nausea or vomiting

Less common or rare

Changes in taste
Dryness, Burning, Itching, or Irritation of the eyes
Increased sensitivity of skin to sunlight
Bloody or black, tarry stools
Colicky or burning abdominal or Stomach pain
Mental depression

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Clofazimine

- Concerns about protracted reddish-brown skin discoloration and possible stigmatization
- Ichythosis

- 75-100% of patients within a few weeks
- Reversible, but may take months to years

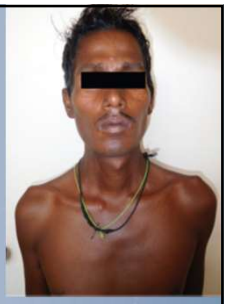

Figure 3: Coppery-red pigmentation due to clofazimine in a patient with leprosy

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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

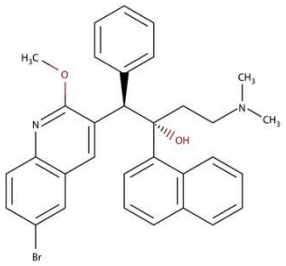

TABLE 1. Pharmacokinetic (PK) parameters of bedaquiline in healthy volunteers, by selected characteristics

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.

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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*)

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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

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- 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

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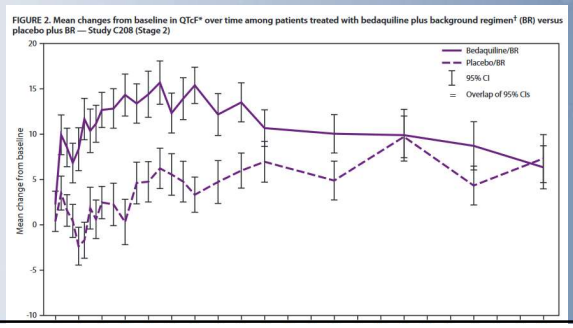
Bedaquiline: Side Effects

- 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

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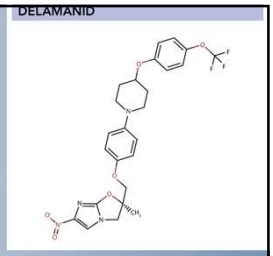
Delamanid



- 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)

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Delamanid


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 7, 2012 VOL. 366 NO. 23

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Maria Tarcela Gler, M.D., Vija Skripconoka, M.D., Epifanio Sanchez-Garavito, M.D., Heping Xiao, M.D., Jose L. Cabrera-Rivero, M.D., Dante E. Vargas-Vasquez, M.D., Mengqiu Gao, M.D., Ph.D., Mohamed Awad, M.B., B.Ch., M.D., Seung-Kyu Park, M.D., Ph.D., Tae Sun Shim, M.D., Ph.D., Gee Young Suh, M.D., Manfred Danilovits, M.D., Hideo Ogata, M.D., Anu Kurve, M.D., Joon Chang, M.D., Ph.D., Katsuhiro Suzuki, M.D., Thelma Tupasi, M.D., Won-Jung Koh, M.D., Barbara Seaworth, M.D., Lawrence J. Geiter, Ph.D., and Charles D. Wells, M.D.

- A randomized placebo-controlled trial involving MDR-TB patients showed that delamanid added to an optimal background regimen significantly increased 2-month sputum culture conversion from 29.6% (placebo) to 45.4% (delamanid 100 mg bd) and 41.9% (delamanid 200 mg bd).
- Delamanid used for more than 6 months significantly increased favorable outcomes (cure or treatment completion) from 55% to 74.5%,and significantly reduced mortality from 8.3%to 1.0%

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Delamanid

- With a **relatively high propensity to develop bacillary drug resistance**, delamanid may be better used with potent companion agents that are less prone to develop bacillary drug resistance, for example, linezolid or bedaquiline

- Substrate of CYP3A4; Caution with like rifampin ritonavir
- **Lack of drug–drug interactions** with major antiretrovirals enables its use in HIV co-infected MDR-TB patients

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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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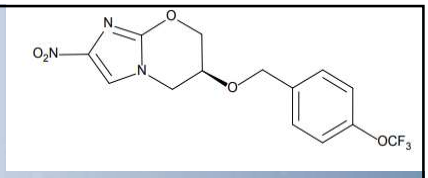
Pretomanid



- 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)

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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 petronamid exposure
- Dolutegravir based: No interaction

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Petronamid: Potential Side Effects

Data from BPaL (Nix-TB trial)

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

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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

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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

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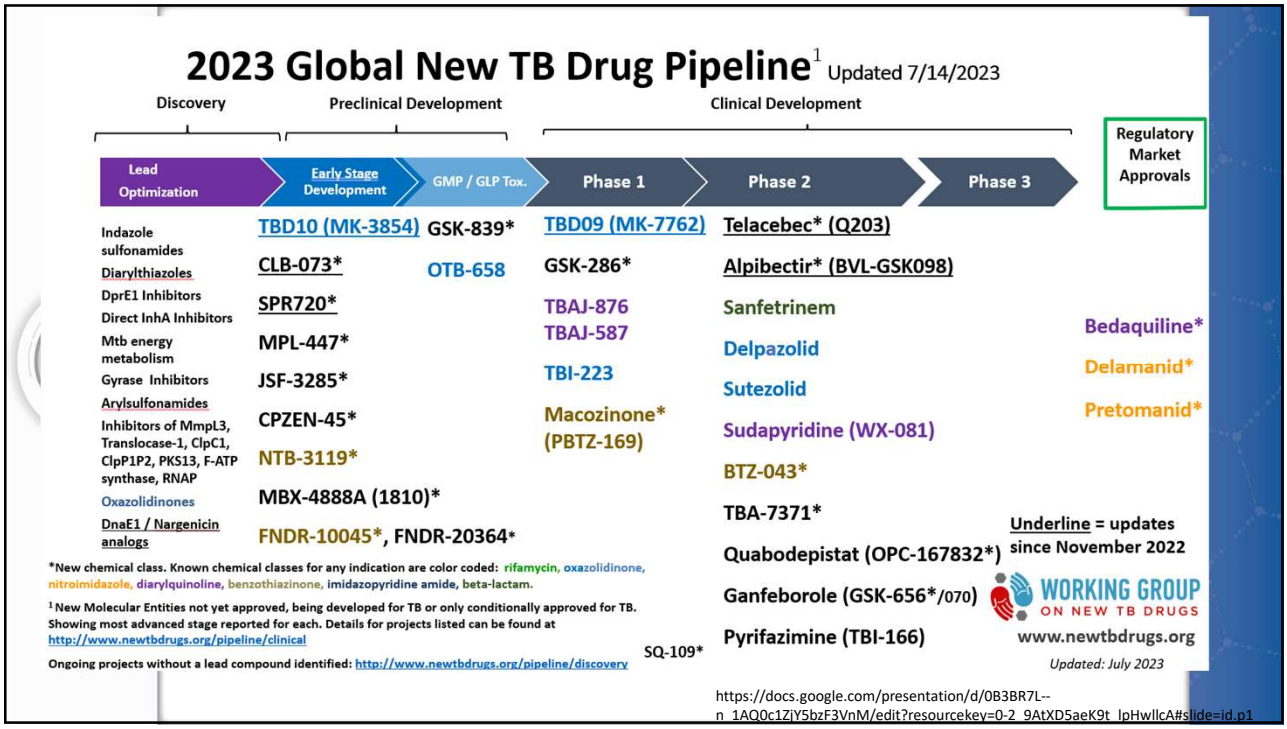

https://docs.google.com/presentation/d/0B3BR7L--n_1AQ0c1ZjY5bzF3VnM/edit?resourcekey=0-2_9AtXD5aeK9t_lpHwllcA#slide=id.p1

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- Thank you for listening!

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