Treatment of TB: Current Drugs in Use

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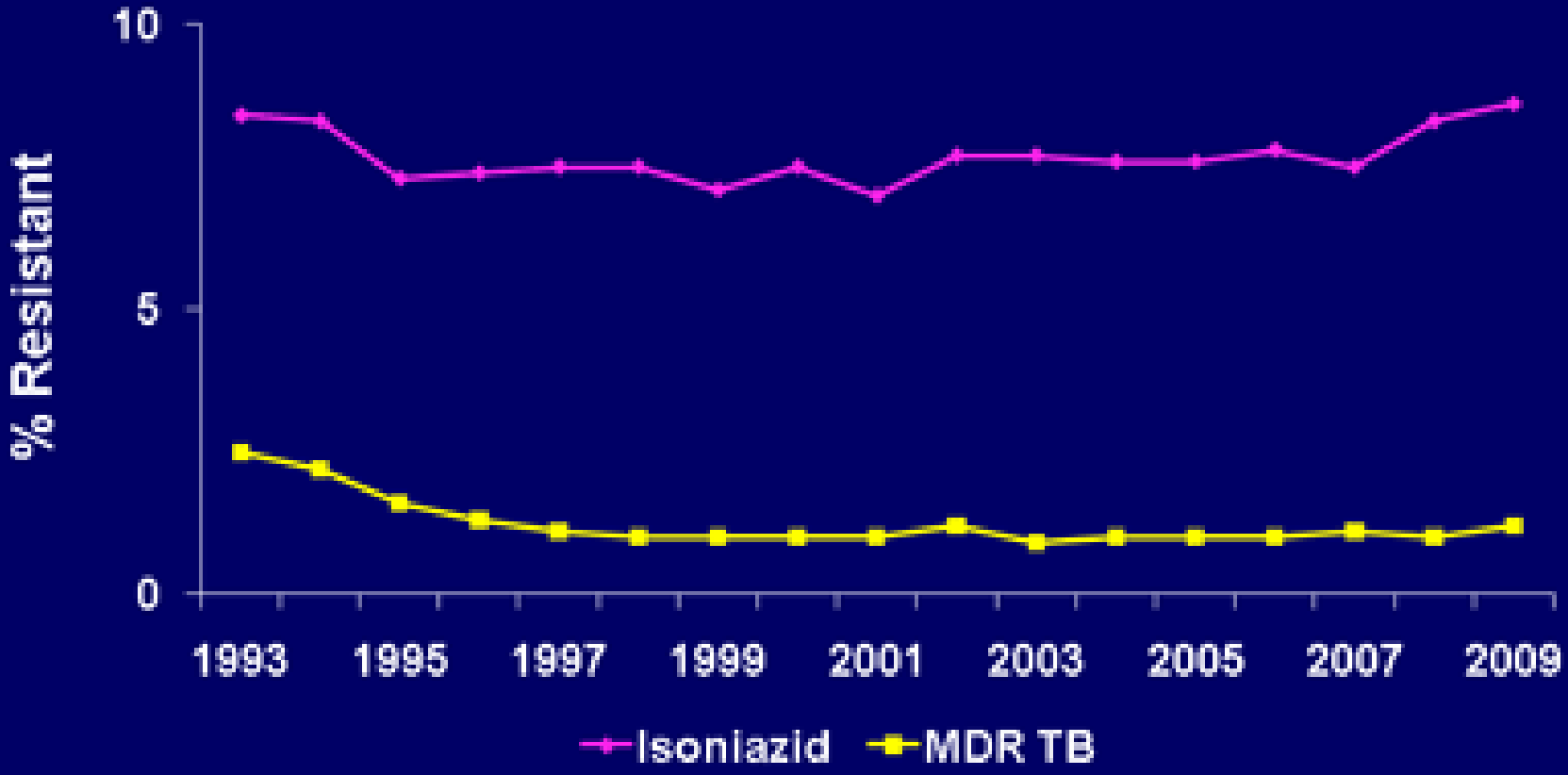
Primary Anti-TB Drug Resistance United States, 1993–2009*



*Updated as of July 1, 2010.

Note: Based on initial isolates from persons with no prior history of TB. Multidrug resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin.

Outline

- Principles
- First-line drugs
  - Fixed-dose combinations
- Commonly used Second-line drugs
- Other Second-line drugs

TB Drugs in Use

First-line

Isoniazid

Rifampin/Rifabutin

Ethambutol

Pyrazinamide

Injectables

Streptomycin

Kanamycin

Amikacin

Capreomycin

Quinolones

Ofloxacin

Levofloxacin

Moxifloxacin

Other 2nd-line

Ethionamide

Cycloserine

PAS

Linezolid

Amox-Clav

Clofazamine

Imipenem

Clarithromycin

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Principles

- Combination therapy
  - Eradicate TB infection
  - Protect against resistance
  - Prevent Relapse
- Weight-based dosing
  - All first-line TB drugs are dosed based on patient's weight
- Directly Observed Therapy

Limitations

- Lack of good information on pediatric pharmacokinetics
  - Utility of serum drug levels

First Line Drugs

Isoniazid (INH)

- **Mechanism:** Affects cell wall synthesis (Bactericidal)
- **Dosing**
  - Adults: 5 mg/kg/d to max 300mg/d; “high dose”: 900-1500 mg twice/thrice weekly
  - Children: 10-15 mg/kg/d to max 300mg/d; 20-30 mg/kg/dose twice/thrice weekly
- **Route:** oral, IV, IM
- **Oral Preparations:** 50/100/300mg scored tablets; 50mg/5ml solution (sorbitol)
- **Metabolism:** Hepatic (cytochrome p450)
- **Adverse Reactions:**
  - Hepatitis (age-related), peripheral neuropathy, hypersensitivity
- **Common Drug Interactions:**
  - Seizure meds: ↑ phenytoin (dilantin); carbamazepine (tegretol) → hepatotoxicity
- **Special circumstances:**
  - Safe during pregnancy, breastfeeding
  - Vitamin B6 (pyridoxine) supplementation

Rifampin

- **Mechanism:** inhibits protein synthesis (Bactericidal)
- **Dosing**
  - Adults: 10 mg/kg/d to max 600mg/d
  - Children: 10-20 mg/kg/d to max 600mg/d
- **Route:** oral, IV
- **Oral Preparations:** 150/300mg capsules
- **Metabolism:** Hepatic (cytochrome p450)
- **Adverse Reactions:**
  - Rash, pruritis, orange body fluids, hepatotoxicity, hematologic, GI upset, flu-like syndrome
- **Common Drug Interactions:**
  - Many HIV medications (protease inhibitors), oral contraceptives, warfarin, methadone, corticosteroids
- **Special circumstances:**
  - Safe during pregnancy, breastfeeding

http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm

Other rifamycins

- Rifabutin
  - 5mg/kg (max 300mg/d)
  - Fewer problematic drug interactions
- Rifapentine
  - Drug interactions similar to rifampin
  - Once weekly regimen with INH for continuation phase for…
    - HIV neg adults, non-cavitary dz, cx neg at 2 months

Pyrazinamide (PZA)

- **Mechanism:** Unclear (Bactericidal inside cells (acidic pH))
- **Dosing**
    - Adults: 25 mg/kg/d to max 2 g/d
    - Children: 20-40 mg/kg/d
- **Route:** oral
- **Oral Preparation:** 500mg scored tablets
- **Metabolism:** Renal
- **Adverse Reactions:**
    - GI upset, hepatitis, gout (hyperuricemia), rash, photosensitivity
- **Common Drug Interactions:** none
- **Special circumstances:**
    - Dose not protect against resistance, allows for short-course therapy
    - Dose-adjust with renal failure
    - Dose based on lean body weight
    - ? Safety in pregnancy

Ethambutol

- **Mechanism:** Inhibits cell wall synthesis (mostly bacteriostatic)
- **Dosing**
    - Adults: 15-20 mg/kg/d
    - Children: 15-20 mg/kg/d
- **Route:** oral
- **Oral Preparations:** 100/400mg scored tablets
- **Metabolism:** Renal
- **Adverse Reactions:**
    - Optic neuritis (dose-related)
- **Common Drug Interactions:** none
- **Special circumstances:**
    - Baseline and monthly visual acuity, color-vision testing
    - Safe during pregnancy, breastfeeding
    - Dose adjust for renal disease

Streptomycin

- **Mechanism:** Inhibits protein synthesis (bactericidal)
- **Dosing**
  - Adults: 15 mg/kg/d 5-7x/wk, then 2-3x/wk
  - Children: 20-40 mg/kg/d
- **Route:** IV, IM
- **Oral Preparations:** none
- **Metabolism:** Renal
- **Adverse Reactions:**
  - Nephrotoxicity, Ototoxicity/Vestibular toxicity (increased with age, prolonged use), Electrolyte abnormalities (hypokalemia, hypomagnesemia), local pain
- **Common Drug Interactions:**
  - Careful with other nephrotoxins (diuretics, NSAIDS)
- **Special circumstances:**
  - Avoided during pregnancy (congenital deafness), can be used during breastfeeding
  - Monitor serum levels, renal function
  - Dose adjust for renal disease, obesity (ideal body weight + 40% excess weight)

Example Case

- 32 yo F with AFB smear+ pulmonary TB

Past Medical History: none
Current Medications: OCP
Weight: 130 lbs (59 kg)

TB med dosing:

R	59kg x 10mg/kg = 590 ~ 600 mg	600mg/59kg = **10.17** mg/kg
I	59 kg x 5 mg/kg = 295 ~ 300 mg	300mg/59kg = **5.08** mg/kg
Z	59kg x 25mg/kg = 1475 ~ 1500 mg	1500mg/59kg = **25.4** mg/kg
E	59kg x 15-20mg/kg = 885-1180 ~ 1200 mg	1200mg/59kg = **20.3** mg/kg

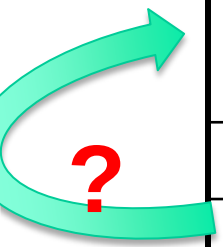
Barrier contraception!

Fixed Dose Combinations (FDC)

- USA
  - Rifamate (RH)
  - Rifater (RHZ)
- Worldwide
  - Many different combinations with different names
    - Rifafour (RHZE)
    - Rifater (RHZ)
    - Rifinah (RH)
    - Ethizide (HE)

Treatment Regimens: LTBI

Adults	Children	
INH 5mg/kg/d x 9 mo	INH 10mg/kg/d x 9 mo	**Max 300 mg/d**
INH 900 mg twice weekly* x 9 mo	INH 20-30 mg/kg twice weekly* x 9 mo	**Max 900 mg/d**
ALTERNATIVE REGIMEN		
Rifampin 600 mg daily x 4 months	Rifampin 10-20 mg/kg/d x 6 months	**Max 600 mg/d**



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*Twice weekly must be administered by DOT

Treatment Regimens: Culture + Pulmonary TB Disease

Initial phase (minimum # doses)	Continuation phase (minimum # doses)	Efficacy
RHZE 5-7 d/wk x 8 wks (40 – 56 doses)	RH 5-7 d/wk x 18 wks (90 – 126 doses)	97-99%
	RH 2-3x/wk x 18 wks (36 - 54 doses)	98%
	H/RPT weekly x 18 wks (18 doses)	97% (HIV neg, non-cavitary, cx neg)

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- Patients with cavitation on CXR, + culture at 2 months require 7 month continuation phase (total 9 months)
- 2x/wk regimens not recommended in resource-limited settings (smaller margin for safety if doses missed) or for advanced HIV+ patients

Alternative Regimens

Initial phase (minimum # doses)	Continuation phase (minimum # doses)	Notes
RHZE 5 - 7 d/wk x 2 wks (10 - 14 doses), then 2x/wk x 12 wks (24 doses)	RH 2x/wk x 18 wks (36 doses) H/RPT weekly x 18 wks (18 doses) (HIV neg, non-cavitary, cx neg)	2x/wk regimens not recommended in resource-limited settings (smaller margin for safety if doses missed) or for advanced HIV+ patients
RHZE 3x/wk x 8 wks (24 doses)	RH 3x/wk x 18 wks (54 doses)	Higher relapse rate in HIV+

•Patients with cavitation on CXR, + culture at 2 months require 7 month continuation phase (total 9 months)

Commonly Used 2nd line Drugs

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Fluoroquinolones

- **Mechanism:** Inhibit DNA gyrase (Bactericidal)
- **Dosing**
  - Adults: Levo: 500-1000 mg/day, Moxi: 400 mg/d
  - Children: Levo: 15-20 mg/kg divided bid, 10 mg/kg/d for older children
- **Route:** oral, IV
- **Oral Preparations:** 250/500/750mg tablets, oral solution (25mg/ml)
- **Metabolism:** Renal
- **Adverse Reactions:**
  - Nausea, headache, tremulousness, arthralgias, rare tendon rupture, prolonged QTc, rare hepatotoxicity
- **Common Drug Interactions:**
  - Avoid administration with milk, antacids,vitamins (iron, zinc, magnesium)
- **Special circumstances:**
  - Generally not used during pregnancy, breastfeeding
  - Dose adjust for renal disease

Injectables (Aminoglycosides)

- **Mechanism:** Inhibit protein synthesis (Bactericidal)
- **Dosing**
  - Adults: 15 mg/kg/d to max of 750-1g; 5-7x/wk, then 2-3x/wk
  - Children: 15-30 mg/kg to max 1g; 5-7x/wk, then 2-3x/wk
- **Route:** IV, IM, [inhalation]
- **Oral Preparations:** none
- **Metabolism:** Renal
- **Adverse Reactions:**
  - Nephrotoxicity, Ototoxicity/Vestibular toxicity (increased with age, prolonged use), Electrolyte abnormalities (hypokalemia, hypomagnesemia)
- **Common Drug Interactions:**
  - Careful with other nephrotoxins (diuretics, NSAIDS)
- **Special circumstances:**
  - Avoided during pregnancy (congenital deafness), can be used during breastfeeding
  - Monitor serum levels, renal function
  - Dose adjust for renal disease, obesity (ideal body weight + 40% excess weight)

Other 2nd line Drugs

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Cycloserine

- **Mechanism:** Inhibits cell wall synthesis (Bacteriostatic)
- **Dosing**
  - Adults: 10-15 mg/kg/d; usually 250mg bid- tid
  - Children: 10-20 mg/kg bid (max 1g daily)
- **Route: Oral**
- **Oral Preparations:** 250mg capsule
- **Metabolism:** Renal
- **Adverse Reactions:**
  - CNS toxicity (poor concentration, lethargy, seizures, psychosis, depression, suicidal ideation), rash, peripheral neuropathy
- **Common Drug Interactions:**
  - May have increased toxicity when ethionamide also used
- **Special circumstances:**
  - All patients should receive vitamin B6 supplementation
  - Best taken on empty stomach (antacids, juice OK)
  - Renal dosing required

Ethionamide

- **Mechanism:** Blocks mycolic acid synthesis (weakly bactericidal)
- **Dosing**
    - Adults: 10-15 mg/kg/d; usually 500-750 mg daily or divided (bid); (max 1g daily)
    - Children: 15-20 mg/kg bid usually divided bid-tid (max 1g daily)
    - Often dose must be ramped up gradually with symptomatic tx of nausea
- **Route: Oral**
- **Oral Preparations:** 250mg tablet
- **Metabolism:** Hepatic
- **Adverse Reactions:**
    - GI upset, anorexia, metallic taste, hepatotoxicity, endocrine effects (hair loss, hypothyroidism gynecomastia), neurotoxicity
- **Common Drug Interactions:**
    - May have increased toxicity when used with cycloserine
- **Special circumstances:**
    - All patients should receive high-dose vitamin B6 supplementation
    - Monitor TSH, LFTs

Para-aminosalicylate (PAS)

- **Mechanism:** Bacteriostatic
- **Dosing**
  - Adults: 8-12 g/d; usually divided bid- tid
  - Children: 200-300 mg/kg/d; usually divided 2-4 times per day
  - Sprinkle granules over applesauce/yogurt or mix in acidic juice
- **Route: Oral**
- **Oral Preparations:** 4g packet
- **Metabolism:** Renal/hepatic
- **Adverse Reactions:**
  - GI distress, reversible hypothyroidism, rare hepatotoxicity/coagulopathy
- **Common Drug Interactions:**
  - Increased risk of hypothyroidism when ethionamide also used
- **Special circumstances:**
  - Packets should be kept in refrigerator/freezer
  - Monitor TSH, electrolytes, blood counts, LFTs
  - Avoid with severe renal failure
  - Shells of the granules can be seen in the stool

Linezolid

- **Mechanism:** Inhibits protein synthesis (? Bacteriocidal)
- **Dosing**
    - Adults: 600mg daily
    - Children: 10 mg/kg tid
- **Route: Oral, IV**
- **Oral Preparations:** 400/600 mg tablet, oral powder for suspension (100mg/5ml)
- **Metabolism:** Renal
- **Adverse Reactions:**
    - Myelosuppression, diarrhea, nausea, optic and peripheral neuropathy, serotonin syndrome
- **Common Drug Interactions:**
    - Do not use with other drugs that increase serotonin levels (anti-depressants)
- **Special circumstances:**
    - All patients should receive vitamin B6 supplementation
    - Avoid in patients with symptoms of neuropathy
    - Monitor CBC

Amoxicillin-Clavulanate

- **Mechanism:** penicillin-beta-lactam inhibitor (? Early bacteriocidal)
- **Dosing**
  - Adults: 2000mg/125mg twice daily
  - Children: 80 mg/kg bid (amoxicillin component)
- **Route: Oral**
- **Oral Preparations:** 1000/62.5 mg tablet (Augmentin XR), 600mg/5ml solution
- **Metabolism:** Renal/hepatic
- **Adverse Reactions:**
  - Diarrhea/abdominal discomfort, nausea/vomiting, rash, hypersensitivity
- **Common Drug Interactions:**
  - Drugs that inhibit renal clearance can increase toxicity
- **Special circumstances:**
  - Use with caution in patients with liver disease
  - Renal dosing required

Clofazamine

- **Mechanism:** in vitro activity (limited in vivo data)
- **Dosing**
  - Adults: 100-200 mg daily
  - Children: 1 mg/k/d
- **Route: Oral**
- **Oral Preparations:** 50/100 mg capsule
- **Metabolism:** Hepatic
- **Adverse Reactions:**
  - Red discoloration of skin, body fluids, GI intolerance, photosensitivity, retinopathy, pruritus, bleeding, bowel obstruction
- **Common Drug Interactions:**
  - May have increased toxicity when ethionamide also used
- **Special circumstances:**
  - Not commercially available in the US, obtain from FDA
  - Not recommended in pregnancy, breastfeeding

Imipenem-cilastatin

- **Mechanism:** beta-lactam, in vitro activity (very limited clinical experience)
- **Dosing**
  - Adults: 1000 mg every 12 hours
  - Children: 20-40 mg/kg IV every 8 hours (meropenem prefered)
- **Route: IV, IM**
- **Oral Preparations:** none
- **Metabolism:** Hepatic
- **Adverse Reactions:**
  - Diarrhea, nausea, vomiting, seizures, transaminitis
- **Common Drug Interactions:**
  - estrogens
- **Special circumstances:**
  - Renal dosing required

Cross-Resistance

Drug	Cross-Resistance	Comments
Isoniazid	Ethionamide	Cross-resistance to ethionamide may occur when there is low-level resistance to isoniazid.
Rifampin	Rifamycins	Cross-resistance among the rifamycin class of drugs is typical. In a few strains that are resistant to rifampin, rifabutin may retain susceptibility *in vitro*.
Ethambutol	None	
Pyrazinamide	None	
Streptomcyin	None	
Amikacin	Kanamycin	High likelihood of cross-resistance since it is associated with the same mutation.
Kanamycin	Amikacin	High likelihood of cross-resistance since it is associated with the same mutation.
Capreomycin	Amikacin/Kanamycin	Variable frequency of cross resistance has been reported.
Fluoroquinolones	Other fluoroquinolones	In general, there is a complete class effect cross-resistance among fluoroquinolones *in vitro*. However, data suggest that moxifloxacin may continue to demonstrate some activity despite *in vitro* resistance to ofloxacin.
Cycloserine	None	
PAS	None	
Ethionamide	Isoniazid	Cross-resistance to isoniazid may occur when there is low-level resistance to ethionamide.
Clofazimine	None	

Treatment of Drug Resistant TB

	Length of treatment	Regimen/ # of drugs	Cure rate	
Pansusceptible	6 months	H/R/Z x 2, H/R x 4	99%	
INH resistance	12 months	2 (R/E)	95%	Z throughout improves outcome, ? FQ
Rifampin resistance	18 months	2 (H/E)	95%	? FQ, ? inject may allow 12 mo.
INH and Rifampin resistance	18-24 months	4 to include injectable and a quniolone	70%	Consider surgery
INH, Rifampin plus	24 months after sputum culture conversion	At least 5 to include an injectable	50-70%	Consider surgery

Thank you for your attention