Chapter IV: Anti-Tuberculosis Drugs in Current Use

A. OVERVIEW 9

B. PRINCIPLES OF COMBINATION CHEMOTHERAPY 10

1. Isoniazid (INH) 14

a. Dose 14

b. Preparations and administration 14

c. Adverse effects 14

d. Use in pregnancy and breastfeeding 15

e. Central Nervous System (CNS) penetration 16

f. Use in renal disease 16

g. Use in hepatic disease 16

h. Monitoring 16

2. Pyridoxine (Vitamin B_6) 16

3. Rifampin (RIF) 17

a. Dose 17

b. Preparations and adminstration 17
c. Adverse effects 17
d. Use in pregnancy and breastfeeding 18
e. CNS penetration 18
f. Use in renal disease 18
g. Use in hepatic disease 19
h. Monitoring 19

4. Rifabutin 19

a. Dose 19
b. Preparations and administration 19
c. Adverse effects 19
d. Use in pregnancy and breastfeeding 20
e. CNS penetration 20
f. Use in renal disease 20
g. Use in hepatic disease 20
h. Monitoring 21

5. Rifapentine 21

a. Dose 21
b. Preparations and administration 21
c. Adverse effects 21
d. Use in pregnancy and breastfeeding 21

e. CNS penetration 22
f. Use in renal disease 22
g. Use in hepatic disease 22
h. Monitoring 22

6. Pyrazinamide (PZA) 23

a. Dose 23
b. Preparations and administration 23
c. Adverse effects 23
d. Use in pregnancy and breastfeeding 24
e. CNS penetration 24
f. Use in renal disease 24
g. Use in hepatic disease 24
h. Monitoring 24

7. Ethambutol (EMB) 25

a. Dose 25
b. Preparations and administration 25
c. Adverse effects 25
d. Use in pregnancy and breastfeeding 26
e. CNS penetration 26
f. Use in renal disease 26
g. Use in hepatic disease 26

h. Monitoring 26

8. Fixed-Dose Combinations (Rifamate & Rifater) 26

a. Adverse effects 27

b. Use in pregnancy and breastfeeding 27

c. CNS penetration 27

d. Use in renal disease 27

e. Use in hepatic disease 27

f. Monitoring 27

D. SECOND-LINE DRUGS 28

1. Cycloserine 28

a. Dose 28

b. Preparations and administration 28

c. Adverse effects 28

d. Use in pregnancy and breastfeeding 28

e. CNS penetration 28

f. Use in renal disease 29

g. Use in hepatic disease 29

h. Monitoring 29

2. Ethionamide 29

a. Dose 29

b. Preparations and administration 29
c. Adverse reactions 30
d. Use in pregnancy and breastfeeding 30
e. CNS penetration 30
f. Use in renal disease 30
g. Use in hepatic disease 30
h. Monitoring 31

3. Streptomycin (SM), injectable 31

a. Dose 31
b. Preparations and administration 31
c. Adverse effects 31
d. Use in pregnancy and breastfeeding 32
e. CNS penetration 32
f. Use in renal disease 32
g. Use in hepatic disease 32
h. Monitoring 32

4. Amikacin and kanamycin, injectable 33

a. Dose 33
b. Preparations and administration 33
c. Adverse effects 33
d. Use in pregnancy and breastfeeding 34

e. CNS penetration 34
f. Use in renal disease 34
g. Use in hepatic disease 34
h. Monitoring 34

5. Capreomycin, injectable 34

a. Dose 34
b. Preparations and administration 35
c. Adverse effects 35
d. Use in pregnancy and breastfeeding 35
e. CNS penetration 35
f. Use in renal disease 35
g. Use in hepatic disease 36
h. Monitoring 36

6. P-Aminosalicylic acid (PAS) 36

a. Dose 36
b. Preparations and administration 36
c. Adverse effects 37
d. Use in pregnancy and breastfeeding 37
e. CNS penetration 37
f. Use in renal disease 37
g. Use in hepatic disease 37

h. Monitoring 38

7. Fluoroquinolones 38

a. Dose 38

b. Preparations and administration (levofloxacin) 38

c. Adverse effects (levofloxacin) 38

d. Use in pregnancy and breastfeeding 39

e. CNS penetration 39

f. Interference with absorption 39

g. Use in renal disease 39

h. Use in hepatic disease 39

i. Monitoring 39

E. DRUG INTERACTIONS 39

1. Interactions Affecting Anti-tuberculosis Drugs 40

a. Rifabutin 40

b. Fluoroquinolones 40

2. Effects of Anti-Tuberculosis Drugs on Other Drugs 40

a. Drug interactions due to rifamycins 40

b. Drug interactions due to isoniazid (INH) 41

c. Drug interactions due to fluoroquinolones 41

F. PREGNANCY AND BREASTFEEDING 42

REFERENCES 43

A. Overview

There are currently 10 drugs approved by the U.S. Food and Drug Administration (FDA) for treating tuberculosis. Though not approved for treating TB, the fluoroquinolones are used commonly to treat drug-resistant TB or for patients who are intolerant to some of the first-line drugs. Rifabutin, not approved for TB, is useful for treating TB in patients also taking medications that have unacceptable interactions with other rifamycins. Amikacin and kanamycin, aminoglycoside drugs, are also used as second-line drugs for treating TB. Streptomycin (SM) once was considered a first-line drug, but because of increasing prevalence of resistance to SM in many parts of the world it is now reserved for special situations such as drug intolerance or resistance.

Anti-tuberculosis Drugs Currently in Use in the United States

First-Line Drugs	Second-line Drugs
Isoniazid (INH)*	Cycloserine*
Rifampin (RIF)*	Ethionamide*
Rifapentine (RPT)*	Levofloxacin
Rifabutin	Moxifloxacin
Ethambutol (EMB)*	Gatifloxacin
Pyrazinamide (PZA)*	p-Aminosalicylic acid (PAS)*
	Streptomycin (SM)*
	Amikacin/Kanamycin
	Capreomycin*
	Linezolid
*FDA approved for TB tx	

B. Principles of Combination Chemotherapy

The goals of anti-tuberculosis chemotherapy are to kill tubercle bacilli rapidly, prevent the emergence of drug resistance, and eliminate persistent bacilli from the host's tissues to prevent relapse. Achieving these goals requires administration of a combination of chemotherapeutic agents with specific activities for a sufficient length of time.

Treatment of TB consists of two phases. During Phase I (first 8 weeks) intensive chemotherapy is given to rapidly kill large, actively multiplying populations of tubercle bacilli. To ensure that at least two and ideally three potent and active drugs are used when baseline resistance may unknowingly be present, 4 drugs are started to ensure rapid killing of the large bacillary populations and prevent the growth of drug-resistant mutants. Phase II (continuation phase of 4 to 7 months, longer if drug-resistant) consists of maintenance chemotherapy directed toward eliminating smaller populations of persisting or "dormant" organisms. During this period, dormant bacilli are killed during their brief spurts of metabolic activity.

It is theorized that there are three separate subpopulations of *M. tuberculosis* within the host. These populations are defined by their growth characteristics and the milieu in which they are located. The largest of the subpopulations consists of rapidly growing extracellular bacilli that reside mainly in cavities. This subpopulation, because of its size, is most likely to harbor organisms with random mutations that confer drug resistance. INH has been shown to possess the most potent ability to kill rapidly multiplying *M. tuberculosis* during the initial part of therapy (early bactericidal activity), thereby rapidly decreasing infectiousness. It is followed by EMB, RIF, and SM. PZA has weak early bactericidal activity during the first 2 weeks of treatment. Drugs that have potent early bactericidal activity reduce the chance of resistance developing within the bacillary population. The rapidly dividing population of bacilli is eliminated early in effective therapy as shown by the early clinical responses and clearing of live bacilli from sputum within 2 months in about 80% of patients.

The remaining subpopulations of *M. tuberculosis* account for treatment failures and relapses, especially when the duration of therapy is inadequate. These residual populations include organisms that are growing more slowly, often in the acidic environment provided by areas of necrosis, and a group that is characterized by having spurts of growth interspersed with periods of dormancy. The sterilizing activity of a drug is defined by its ability to kill bacilli, mainly in these two subpopulations that persist beyond the early months of therapy, thus decreasing the risk of relapse. Rifampin and PZA have the greatest sterilizing activity followed by INH and SM. The sterilizing activity of rifampin persists throughout the course of therapy while PZA provides additive sterilizing activity only during the initial 8 weeks of therapy and is required for all courses with a six-month duration of therapy.

The key to a successful tuberculosis treatment regimen is multi-drug therapy designed to prevent acquired drug resistance, particularly in the face of unexpected initial drug resistance to one or two first-line drugs. Because of the relatively high proportion of adult patients with INH-resistant tuberculosis, 4 drugs are necessary in the *initial phase* for the 6-month regimen to be maximally effective. Thus, in most circumstances, the treatment regimen for all adults with previously untreated tuberculosis should consist of an 8 week initial phase of INH, RIF, PZA, and EMB. If drug susceptibility test results are known and the organisms are fully susceptible, EMB may be discontinued if therapy is administered daily. There is limited data on this approach with intermittent therapy as most clinical trials included EMB for the initial 8 weeks of therapy. EMB may be discontinued during intermittent therapy among patients at low risk for poor treatment outcomes. For children whose visual acuity cannot be monitored, EMB is usually not recommended except when there is an increased likelihood of the disease being caused by INH-resistant organisms or when the child has "adult type" tuberculosis (upper lobe infiltration, cavity formation). If PZA cannot be included in the *initial phase* of treatment, or the isolate is resistant to PZA (but not the other first line agents), the *initial phase* should consist of INH, RIF, and EMB given for the 8 week *initial phase* of treatment followed by 31 weeks of INH plus RIF. Examples of circumstances in which PZA may be withheld include severe liver disease, gout, and pregnancy.

📖 For more information on specific regimens, selection of specific patients for intermittent dosing regimens and when daily, once, twice or three-times a week dosing is used, see *Chapter III Latent TB Infection (LTBI) Treatment and Follow-up* and *Chapter VI Treatment and Follow-up for Suspect and Active TB Disease*.

C. First-Line Drugs

DOSES*OF FIRST-LINE ANTITUBERCULOSIS DRUGS FOR ADULTS AND CHILDREN†0

Drug	Preparation	Adults/children	Doses			
			Daily	1x/wk	2x/wk	3x/wk
INH	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 ml); aqueous solution (100 mg/ml) for intramuscular injection¶	Adults (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
		Children (max.)	10–15 mg/kg (300 mg)	—	20–30 mg/kg (900 mg)	—
RIF	Capsule (150 mg, 300 mg); powder may be suspended for oral administration; aqueous solution for intravenous injection	Adults‡ (max.)	10 mg/kg (600 mg)	—	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children (max.)	10–20 mg/kg (600 mg)	—	10–20 mg/kg (600 mg)	—

Definitions of abbreviations: EMB = ethambutol; FDA = Food and Drug Administration; INH = isoniazid; PZA = pyrazinamide; RFB = rifabutin; RIF = rifampin; RPT = rifapentine.

* Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.

† For the purposes of this document, adult dosing begins at the age of 15 years.

¶ INH is used, but not FDA-approved, for intravenous administration. For intravenous use of INH, please consult with *CDPHE's Nurse Consultant* at *303-692-2656*

‡ Dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

§ The drug can likely be used safely in older children but should be used with caution in children less than 5 years of age, in whom visual acuity cannot be monitored. In younger children, EMB at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to INH or RIF.

Drug	Preparation	Adults/children	Daily	1x/wk	2x/wk	3x/wk
RFB	Capsule (150 mg)	Adults‡ (max.)	5 mg/kg (300 mg)	__	5 mg/kg (300 mg)	5 mg/kg (300 mg)
		Children	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown
RPT	Tablet (150 mg, film coated)	Adults	__	15 mg/kg (continuation phase) (900 mg)^^	__	__
		Children	This drug is not approved for use in children	This drug is not approved for use in children	This drug is not approved for use in children	This drug is not approved for use in children
PZA	Tablet (500 mg, scored)	Adults	See Table 5	__	See Table 5	See Table 5
		Children (max.)	15–30 mg/kg (2.0 g)	__	50 mg/kg (2.0 g)	__
EMB	Tablet (100 mg, 400 mg)	Adults	See Table 6	__	See Table 6	See Table 6
		Children§ (max.)	15–20 mg/kg daily (1.0 g)	__	50 mg/kg (2.5 g)	__

Definitions of abbreviations: EMB = ethambutol; FDA = Food and Drug Administration; INH = isoniazid; PZA = pyrazinamide; RFB = rifabutin; RIF = rifampin; RPT = rifapentine.

* Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.

† For the purposes of this document, adult dosing begins at the age of 15 years.

¶ INH is used, but not FDA-approved, for intravenous administration. For intravenous use of INH, please consult with *CDPHE's Nurse Consultant* at *303-692-2656*

‡ Dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

^^See text page 21 for dose increase from 10 to 15 mg/Kg.

§ The drug can likely be used safely in older children but should be used with caution in children less than 5 years of age, in whom visual acuity cannot be monitored. In younger children, EMB at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to INH or RIF.

Source: ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):4

1. Isoniazid (INH)

Isoniazid (INH) is a first-line drug for treatment of all forms of tuberculosis caused by organisms known or presumed to be susceptible to the drug. INH has its greatest impact against rapidly dividing mycobacteria due to its early bactericidal activity.

a. Dose

ADULTS (maximum): 5 mg/kg (300 mg) **daily** or 15 mg/kg (900 mg) **once, twice,** or **three times weekly**.

CHILDREN (maximum): 10-15 mg/kg (300 mg) **daily** or 20-30 mg/kg (900 mg) **twice weekly**.

b. Preparations and administration

CDPHE's Apothecary offers tablets (100 mg, 300 mg); suspension (50 mg/5 ml; **not currently available**) for oral administration.

c. Adverse effects

Asymptomatic elevation of aminotransferases (ALT and AST): Aminotransferase elevations up to 5 times the upper limit of normal occur in 10-20% of persons receiving INH alone for treatment of latent tuberculosis infection. The enzyme levels usually return to normal even with continued administration of the drug.

Clinical hepatitis: Incidence of clinical hepatitis is low. For INH alone the risk increases with increasing age. It is uncommon in persons less than 20 years of age but is found in nearly 2% in persons aged 50-64 years. The risk also may be higher in persons with underlying liver disease, in those with a history of heavy alcohol consumption and in women during pregnancy or the early postpartum period, particularly among Hispanic women.

Fatal hepatitis: Recent studies have shown the rate to be low (0.023% or lower). The risk may be higher in women. Death has been associated with continued administration of INH following onset of symptoms of hepatitis.

Peripheral neurotoxicity: This adverse effect is dose-related and is uncommon (less than 0.2%) at conventional doses. The risk is higher in persons with other conditions that may be associated with neuropathy such as nutritional deficiency, diabetes, HIV infection, renal failure, and alcoholism. Pyridoxine (Vitamin B_6) supplementation (25 – 50 mg/day) is recommended for patients with these conditions to help prevent neuropathy. Pyridoxine (Vitamin B_6) is also recommended for pregnant and breastfeeding women to minimize the risk of neurotoxicity for the baby.

Central nervous system effects: Effects such as dysarthria, irritability, seizures, dysphoria, and an inability to concentrate have been reported but have not been quantified.

Lupus-like syndrome: Approximately 20% of patients receiving INH develop anti-nuclear antibodies. Less than 1% develop clinical lupus erythematosis which necessitates drug discontinuation.

Hypersensitivity reactions: Reactions such as fever, rash, Stevens-Johnson syndrome, hemolytic anemia, vasculitis, and neutropenia are rare.

Monoamine (histamine/tyramine) poisoning: There are reports of occurrences after ingestion of foods and beverages with high monoamine content but it is rare. If flushing occurs, patients should be instructed to avoid foods and drinks such as certain cheeses and wine having high concentrations of monoamines.

Diarrhea: The commercial liquid preparation of INH, because it contains sorbitol, is associated with diarrhea.

Drug interactions: INH can increase concentrations of some drugs to the point of toxicity, especially the anticonvulsants phenytoin (Dilantin) and carbamazepine (Tegretol). INH may also increase the concentrations of benzodiazepines such as diazepam and triazolam. Rifampin has the opposite effect on the serum concentration of many of these drugs. The combined effect of rifampin and INH is usually a decrease in the concentration of the drugs such as phenytoin and diazepam.

Isoniazid may increase toxicity of the following drugs, but these potential interactions have not been well studied: acetaminophen, valproate, serotonergic antidepressants, disulfiram, warfarin, and theophylline.

Some publications recommend against the use of INH for persons taking disulfiram (Antabuse). There is no strong evidence that taking disulfiram and INH together causes a serious health risk. A study done in Denver demonstrated less liver injury among alcoholics willing to receive disulfiram than those who continued to drink alcohol.

d. Use in pregnancy and breastfeeding

INH crosses the placenta but is considered safe in pregnancy. The risk of hepatitis may be increased in the peripartum period. Pyridoxine (Vitamin B_6) supplementation (25 mg/day) is recommended if INH is given during pregnancy. It should be noted that multivitamin preparations have variable amounts of pyridoxine but generally less than 25 mg/day and, thus, do not provide adequate supplementation. Breastfeeding is not contraindicated when the mother is being treated with INH. The amount of INH provided by breast milk is inadequate for treatment of the infant.

e. Central Nervous System (CNS) penetration

Penetration is excellent. Cerebrospinal fluid (CSF) concentrations are similar to concentrations achieved in serum.

f. Use in renal disease

INH can be used safely without dose adjustment in patients with renal insufficiency and end-stage renal disease that requires chronic hemodialysis.

📖 For more information, see Section G Renal Insufficiency and End Stage Renal Disease in *Chapter VIII: Treatment in Special Situations*.

g. Use in hepatic disease

The risk of drug accumulation and drug-induced hepatitis may be increased in the presence of hepatic disease; however, INH may be used in patients with stable hepatic disease. Laboratory and clinical monitoring should be more frequent in such situations.

📖 For more information, see Section H., "Hepatic Disease" in *Chapter VIII: Treatment in Special Situations*.

h. Monitoring

Patients receiving INH should receive monthly clinical monitoring. Routine laboratory monitoring is not necessary for all patients. Baseline and follow-up serum ALT and bilirubin are recommended for patients with a possible liver disorder; those with a history of chronic liver disease (e.g., chronic hepatitis B and C, alcoholic hepatitis, and cirrhosis), patients with chronic use of alcohol, those with HIV infection treated with highly active antiretroviral treatment (HAART), pregnant women, and those who are up to 3 months postpartum. Liver enzymes should be obtained at baseline and repeated for monitoring if elevated or if symptoms of hepatitis or drug toxicity (e.g. rash) develop.

Serum concentrations of phenytoin and carbamazepine may be increased in persons taking INH. However, in combination therapy with RIF, the effects of INH on serum concentrations of the anticonvulsants are limited by the decrease caused by RIF. Thus, it is important to measure serum concentrations of these drugs in patients receiving INH with or without RIF and adjust the dose if necessary.

2. Pyridoxine (Vitamin B_6)

Peripheral neuropathy is associated with the use of INH but is uncommon at doses of 5 mg/kg. Persons with conditions in which neuropathy is common (e.g., diabetes, uremia, alcoholism, malnutrition, HIV-infection) as well as pregnant women, persons with a seizure disorder, infants who are strictly breastfeeding, individuals with diets deficient in

pyridoxine, and those with paresthesias while taking INH may be given pyridoxine (Vitamin B_6) at a dosage of 10-50 mg/day with INH.

3. Rifampin (RIF)

Rifampin (RIF) is a first-line drug for treatment of all forms of tuberculosis caused by organisms with known or presumed sensitivity to the drug. It has activity against organisms that are dividing rapidly (early bactericidal activity) and against semi-dormant bacterial populations, thus accounting for its sterilizing activity. RIF is an essential component of all short-course regimens.

a. Dose

ADULTS (maximum): 10 mg/kg (600 mg) **once daily, twice weekly,** or **three times weekly**.

CHILDREN (maximum): 10-20 mg/kg (600 mg) **once daily** or **twice weekly**.

b. Preparations and adminstration

Capsules (150 mg, 300 mg). The contents of the capsule may also be mixed in an appropriate diluent to prepare an oral suspension. Aqueous solution for intravenous administration is available but can be difficult to obtain.

c. Adverse effects

Cutaneous reactions: Pruritis with or without rash may occur in as many as 6% of patients but is generally self-limited. This reaction may not represent true hypersensitivity and continued treatment with the drug may be possible. More severe, true hypersensitivity reactions are uncommon.

Gastrointestinal reactions (nausea, anorexia, abdominal pain): The incidence is variable, but symptoms are rarely severe enough to necessitate discontinuation of the drug.

Flu-like syndrome: Symptoms are more likely to occur with intermittent administration of a higher dose.

Hepatotoxicity: Transient asymptomatic hyperbilirubinemia and more severe clinical hepatitis may occur in patients receiving the drug. Hepatitis is more common when the drug is given in combination with INH (2.7%) than when given alone (nearly 0%) or in combination with drugs other than INH (1.1%).

Severe immunologic reactions: In addition to cutaneous reactions and flu-like syndrome, other reactions thought to be immune-mediated include: thrombocytopenia, hemolytic anemia, acute renal failure, and thrombotic

thrombocytopenic purpura. These reactions are rare, each occurring in less than 0.1% of patients.

Orange discoloration of bodily fluids (sputum, urine, sweat, tears): This is a universal effect of the drug. Patients should be warned of this effect at the time treatment is begun. Soft contact lenses and clothing may be permanently stained.

Drug interactions due to induction of hepatic microsomal enzymes: There are a number of drug interactions with potentially serious consequences. Of particular concern are reductions, often to ineffective levels, in serum concentrations of common drugs, such as oral contraceptives, methadone, HIV protease inhibitors, and warfarin (coumadin).

📖 For more information, see section E., in this chapter, "*Drug Interactions*".

In addition there are important bi-directional interactions between rifamycins and antiretroviral agents.

📖 Because information on rifamycin drug interactions is evolving rapidly, consult the CDC web site for the latest information.

www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/roleofrifamycins.htm

Effects on urine testing for drug use: There is some cross-reactivity and false-positive urine screening tests for opiates in patients receiving rifampin when using the Kinetic Interaction of Microparticles in Solution (KIMS) method (e.g., Abuscreen OnLine opiates assay, Roche Diagnostic Systems). Confirmatory tests, such as gas chromatography/mass spectrometry will distinguish rifampin from opiates.

d. Use in pregnancy and breastfeeding

Rifampin crosses the placenta but is not known to have teratogenic effects in humans and is considered safe in pregnancy. Breastfeeding while on rifampin is considered safe.

e. CNS penetration

Concentrations in the CSF may be only 10-20% of serum levels, but this is sufficient for clinical efficacy. Penetration may be improved in the setting of meningitis.

f. Use in renal disease

RIF can be used safely without dose adjustment in patients with renal insufficiency and end-stage renal disease.

📖 For more information, see section G., "Renal Insufficiency and End Stage Renal Disease" in *Chapter VIII: Treatment in Special Situations*.

g. Use in hepatic disease

Drug clearance may be impaired in the presence of liver disease, causing increased serum levels. However, because of the critical importance of rifampin in all short-course regimens, it generally should be included, but the frequency of clinical and laboratory monitoring should be increased.

📖 See section H., "Hepatic Disease" in *Chapter VIII: Treatment in Special Situations.*

h. Monitoring

Routine monitoring tests are not required. However, rifampin causes many drug interactions that may necessitate regular measurements of the serum concentrations of the drugs in question.

4. Rifabutin

Rifabutin is used as a substitute for rifampin in the treatment of all forms of tuberculosis caused by organisms that are known or presumed to be susceptible to this drug. The drug is generally reserved for patients who are receiving any medication having unacceptable interactions with rifampin (e.g. HIV patients). Some patients with intolerance to rifampin may tolerate rifabutin, but this should not be attempted in patients with hypersensitivity or other severe reactions to rifampin.

a. Dose

ADULTS (maximum): 5 mg/kg (300 mg) **daily, twice weekly**, or **three times weekly**. The dose may need adjustment when used with protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

CHILDREN (maximum): Appropriate dosing for children is unknown.

📖 Because information on rifamycin drug interactions is evolving rapidly, consult the CDC web site: www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/roleofrifamycins.htm to obtain the latest information.

b. Preparations and administration

Capsules (150 mg) for oral administration

c. Adverse effects

Hematologic toxicity: Neutropenia severe enough to necessitate discontinuation of the drug is dose-related, occurring more frequently with daily than with intermittent administration of the same dose. In several studies of patients with and without HIV infection, neither neutropenia nor thrombocytopenia was associated with rifabutin.

Uveitis: This is a rare complication when the drug is given alone at a standard (300 mg daily) dose. The occurrence is higher with higher doses or when rifabutin is used in combination with macrolide antimicrobial agents, protease inhibitors, and azole antifungal agents that reduce its clearance.

Gastrointestinal symptoms: Symptoms occurred in 3% of patients with advanced HIV infection given 300 mg/day. In subsequent studies, no increased incidence of gastrointestinal symptoms was noted among patients taking rifabutin.

Polyarthralgias: This symptom is more common at higher doses.

Hepatotoxity: Asymptomatic elevation of liver enzymes has been reported at a frequency similar to that of RIF. Clinical hepatitis occurs in less than 1% of patients receiving the drug.

Pseudojaundice (skin discoloration with normal bilirubin): This is usually self-limited and resolves with discontinuation of the drug.

Rash: Rash is only rarely associated with rifabutin.

Flu-like syndrome: Flu-like syndrome is rare in patients taking rifabutin

Orange discoloration of bodily fluids (sputum, urine, sweat, tears): This is a universal effect of the drug. Patients should be warned of this effect at the time treatment is begun. Soft contact lenses and clothing may be permanently stained.

d. Use in pregnancy and breastfeeding

There are insufficient data on the use of rifabutin in pregnant and lactating women. The drug should be used with caution in pregnancy and breastfeeding.

e. CNS penetration

The drug penetrates inflamed meninges.

f. Use in renal disease

Rifabutin may be used without dosage adjustment in patients with renal insufficiency and end-stage renal disease.

📖 For more information see Section G., "Renal Insufficiency and End Stage Renal Disease" in *Chapter VIII: Treatment in Special Situations*.

g. Use in hepatic disease

The drug should be used with increased clinical and laboratory monitoring in patients with underlying liver disease. Dose reduction may be necessary in patients with severe liver dysfunction.

📖 For more information, see section H., "Hepatic Disease" in *Chapter VIII: Treatment in Special Situations*.

h. Monitoring

Monitoring is similar to that recommended for rifampin. Although drug interactions are less problematic with rifabutin, they still occur and close monitoring is required.

5. Rifapentine

Rifapentine may be used once weekly with INH in the continuation phase of treatment for HIV-negative patients with non-cavitary, drug-susceptible pulmonary tuberculosis that have negative sputum smears at completion of the initial phase of treatment.

a. Dose

ADULTS (maximum): 18 mg/kg (900 mg), **once weekly** for continuation phase.

Suggested Rifapentine Doses for Adults 40 Kg or Greater

	Weight (kg)		
	Less than 40 kg	**41 - 50 kg**	**51 kg or greater**
Once weekly	600 mg (max 15 mg/kg)	750 mg (15 to 18 mg/kg)	900 mg (max 18 mg/kg)

The dose of 900 mg Rifapentine once weekly given with 900 mg INH has been used in the published study of over 4,000 adults in a comparative study involving patients randomized to receive 16-week continuation phase with either INH plus rifampin twice-weekly and INH plus rifapentine given once-weekly.

CHILDREN: **The drug is not approved for use in children.**

b. Preparations and administration

Tablet (150 mg film-coated) for oral administration.

c. Adverse effects

The adverse effects of rifapentine are similar to those associated with rifampin. Rifapentine is an inducer of multiple hepatic enzymes and therefore may increase metabolism of co-administered drugs that are metabolized by these enzymes.

📖 For more information, see section E., "Drug Interactions" in this chapter.

d. Use in pregnancy and breastfeeding

There is not enough information to recommend rifapentine for pregnant and lactating women.

e. CNS penetration

There are no data on CSF concentrations of rifapentine. There are no data on the use of rifapentine with CNS or skeletal TB.

f. Use in renal disease

Rifapentine has not been evaluated in patients with renal impairment.

📖 For more information, see section G, Renal Insufficiency and End Stage Renal Disease in *Chapter VIII: Treatment in Special Situations*.

g. Use in hepatic disease

The clinical significance of impaired hepatic function with rifapentine is not known.

📖 For more information, see section H., "Hepatic Disease" in *Chapter VIII: Treatment in Special Situations*.

h. Monitoring

Monitoring is similar to that for rifampin. Drug interactions involving rifapentine are being investigated and are likely to be similar to those of rifampin.

6. Pyrazinamide (PZA)

Pyrazinamide (PZA) is a first-line drug for the treatment of all forms of tuberculosis caused by organisms with known or presumed susceptibility to the drug. The drug is believed to exert greatest activity against the population of dormant or semi-dormant organisms contained within macrophages or the acidic environment of caseous foci. Daily-dose recommendations were revised downward in 2003, closer to doses previously recommended by the World Health Organization (WHO). PZA is less effective than INH or EMB as a companion drug in preventing acquired rifampin resistance. It is important to avoid unintentionally treating patients with a regimen in which only rifampin and PZA are the active drugs.

a. Dose

Suggested PZA Doses Using Whole Tablets for Adults 40-90 Kg

	Weight (kg)*		
	40-55 kg	**56-75 kg**	**76-90 kg**
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

CHILDREN (maximum): 15-30 mg/kg (2,000 mg) **daily** or 30-40 mg/kg (2,000 mg) **three times weekly** or 50 mg/kg (2,000 mg) **twice weekly**.

b. Preparations and administration

Tablets (500 mg, scored) for oral administration

c. Adverse effects

Hepatotoxicity: Liver toxicity has been less common with doses of 25 mg/kg per day than was seen with much higher doses. However, PZA appears to be the most common cause of hepatotoxicity in patients receiving standard multi-drug treatment for active TB.

Gastrointestinal symptoms (nausea, vomiting): Mild anorexia and nausea are common at standard doses. Vomiting and severe nausea are less common.

Non-gouty polyarthralgia: Polyarthralgias may occur in up to 40% of patients receiving daily doses of PZA. This rarely requires dosage adjustment or discontinuation of the drug. The pain usually responds to aspirin or other nonsteroidal anti-inflammatory agents.

Asymptomatic hyperuricemia: This is an expected effect of the drug and is generally without adverse consequence.

Acute gouty arthritis: Acute gout is rare except in patients with preexisting gout, generally a contraindication to the use of the drug.

Transient morbilliform rash: This is usually self-limited and is not an indication for discontinuation of the drug.

Dermatitis: PZA may cause photosensitive dermatitis.

d. Use in pregnancy and breastfeeding

PZA is not generally recommended for use in pregnancy in the U.S. because of limited available information about its safety. The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommend this drug for use in pregnant women as it is not known to have teratogenic effects in humans and is likely safe during pregnancy. It is not known whether it is safe for lactating women.

e. CNS penetration

The drug passes freely into the CSF, with concentrations equivalent to serum.

f. Use in renal disease

PZA is primarily cleared by the liver, but its metabolites are excreted in the urine and may accumulate in patients with renal insufficiency. The dose may need to be reduced in patients with renal insufficiency. The risk of hyperuricemia caused by PZA is increased in patients with renal insufficiency.

📖 For more information, see Section G, Renal Insufficiency and End Stage Renal Disease in *Chapter VIII: Treatment in Special Situations.*

g. Use in hepatic disease

PZA can cause liver injury that may be severe and prolonged. If the drug is used in patients with underlying liver disease, laboratory and clinical monitoring should be increased.

📖 For more information, see section H., "Hepatic Disease" in *Chapter VIII: Treatment in Special Situations.*

h. Monitoring

Serum uric acid measurements are not recommended routinely, but may serve as a surrogate marker for compliance. Liver chemistry monitoring should be performed

at baseline and at least monthly when the drug is used in patients with underlying liver disease or when it is used with rifampin in treating latent tuberculosis infection.

7. Ethambutol (EMB)

Ethambutol (EMB) is a first-line drug for treating all forms of tuberculosis. It is included in initial treatment regimens primarily to prevent emergence of rifampin resistance when primary resistance to INH may be present. Ethambutol is generally not recommended for use in children whose visual acuity cannot be monitored (generally under age 5). However, if a child has adult-type tuberculosis or disease that is suspected or proven to be resistant to either INH or rifampin, EMB should be used.

a. Dose

ADULTS: 15-20 mg/kg (1,600 mg) **daily** or 25-35 mg/kg (2,400 mg) **three times weekly** or 40-50 mg/kg (4,000 mg) **twice weekly**.

Suggested EMB Doses Using Whole Tablets for Adults 40-90 Kg

	Weight (kg)*		
	40-55 kg	**56-75 kg**	**76-90 kg**
Daily, mg (mg/kg)	800 (14.5-20.0)	1,200 (16-21.4)	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

CHILDREN (maximum): 15-20 mg/kg (1,000 mg) **daily** or 30 mg/kg (2,000 mg) **three times weekly** or 50 mg/kg (2,500 mg) **twice weekly**. The drug can be used safely in older children but should be used with caution in children when visual acuity cannot be monitored.

b. Preparations and administration

Tablets (100 mg, 400 mg) for oral administration

c. Adverse effects

Retrobulbar neuritis: Manifested as decreased visual acuity or decreased red-green color discrimination affecting one or both eyes. The effect is dose related, with minimal risk at a daily dose of 15 mg/kg. The risk of optic toxicity is increased at higher daily doses and in patients with renal insufficiency. Higher doses can be given safely twice or three times weekly.

Peripheral neuritis: This is a rare adverse effect.

Cutaneous reactions: Skin reactions requiring discontinuation of the drug are rare.

d. Use in pregnancy and breastfeeding

Ethambutol crosses the placenta but is not known to have teratogenic effects in humans (including ophthalmic) and is considered safe in pregnancy. It is safe for lactating women and their infants.

e. CNS penetration

EMB penetrates the meninges and is used in multidrug therapy of TB meningitis but its contribution to efficacy is unknown.

f. Use in renal disease

EMB is primarily cleared by the kidneys. The dose or dosing interval should be adjusted when the creatinine clearance is less than 70 ml/minute. EMB should be administered at a dose of 15-20 mg/kg three times a week by Directly Observed Therapy (DOT) after dialysis in patients with end-stage renal disease.

📖 For more information, see Section G, Renal Insufficiency and End Stage Renal Disease in *Chapter VIII: Treatment in Special Situations*.

g. Use in hepatic disease

EMB is safe with hepatic disease.

📖 For more information, see Section H, Hepatic Disease in *Chapter VIII: Treatment in Special Situations*.

h. Monitoring

Patients should have baseline visual acuity (Snellen) http://www.mdsupport.org/snellen.html and color discrimination (Ishihara) tests http://colorvisiontesting.com/ishihara.htm. At each monthly visit, patients should be asked about visual disturbances. Monthly visual acuity and color discrimination testing is recommended for patients taking doses greater than 15-20 mg/kg, those receiving the drug for longer than 2 months, and anyone with renal insufficiency. Patients should be advised to contact their county health department immediately if they experience a change in vision. EMB should be discontinued immediately and permanently if there are any signs of visual toxicity.

8. Fixed-Dose Combinations (Rifamate & Rifater)

Fixed-dose combination preparations minimize inadvertent monotherapy and may decrease the frequency of acquired drug resistance and medication errors. These preparations should generally be used when therapy cannot be administered under

Directly Observed Therapy (DOT). The use of fixed dose formulations may reduce the number of pills that must be taken daily. Drugs are combined in proportions compatible with daily treatment regimens.

Rifamate: As sold in North America, each capsule contains RIF (300 mg) and INH (150 mg). The daily dose is two capsules (600 mg of RIF and 300 mg of INH). Two capsules of Rifamate plus two 300-mg tablets of INH are used by some programs for intermittent therapy given twice weekly as DOT.

Rifater: Each tablet contains RIF (120 mg), INH (50 mg), and PZA (300 mg). The daily dose is based on weight as follows: 44 kg or less, four tablets; 45-54 kg, five tablets; 55 kg or more, six tablets. To obtain an adequate dose of PZA in persons weighing more than 90 kg, additional PZA tablets must be given.

a. Adverse effects

See comments under individual drugs above.

b. Use in pregnancy and breastfeeding

Rifamate may be used in daily treatment of pregnant women. Rifater should not be used because it contains PZA.

c. CNS penetration

See comments under individual drugs above.

d. Use in renal disease

Rifamate may be used in persons with renal insufficiency. Rifater should not be used because of the potential need to adjust the dose of PZA.

📖 For more information, see section G., "Renal Insufficiency and End Stage Renal Disease" in *Chapter VIII: Treatment in Special Situations.*

e. Use in hepatic disease

In patients with underlying hepatic disease it is advisable to treat with single-drug formulations until safety in an individual patient can be determined and a stable regimen established.

📖 For more information, see section H., Hepatic Disease in *Chapter VIII: Treatment in Special Situations.*

f. Monitoring

See comments under individual drugs above.

D. Second-Line Drugs

NOTE: Second-line TB drugs should be used only in close consultation with a TB medical expert.

1. Cycloserine

Cycloserine is a second-line drug that is used for treating patients with drug-resistant tuberculosis caused by organisms with known or presumed susceptibility to the drug. It may also be used on a temporary basis for patients with acute hepatitis in combination with other non-hepatotoxic drugs.

a. Dose

ADULTS (maximum): 10-15 mg/kg **daily** (1,000 mg), usually 500-750 mg/day. Single daily dosing is preferred but twice daily dosing may be used. Toxicity is more common at doses over 500 mg/day. There are no data to support intermittent administration.

CHILDREN (maximum): 10-15 mg/kg **daily** (1.0 g/day).

b. Preparations and administration

Capsules (250 mg) for oral administration

c. Adverse effects

Central nervous system effects: The central nervous system effects range from mild reactions, such as headache or restlessness, to severe reactions, such as depression, psychosis, and seizures. The drug may exacerbate underlying seizure disorders or mental illness. Seizures have been reported to occur in up to 16% of patients receiving 500 mg twice daily but in only 3% when receiving 500 mg once daily. Pyridoxine may help prevent and treat neurotoxic side effects and is usually given in a dosage of 100-200 mg/day. Rarely cycloserine may cause peripheral neuritis.

d. Use in pregnancy and breastfeeding

Cycloserine crosses the placenta. There are limited data on safety in pregnancy. Thus, it should be used in pregnant women only when there are no suitable alternatives.

e. CNS penetration

Concentrations in CSF approach those in serum.

f. Use in renal disease

The drug can accumulate in patients with impaired renal function and should be used cautiously in such patients. Generally, the dose should be reduced and serum concentrations measured. Cycloserine should not be used in patients having a creatinine clearance of less than 50 ml/minute unless the patient is receiving hemodialysis. For patients being hemodialyzed, the dose should be 500 mg three times a week or 250 mg daily. Serum concentrations of the drug should be measured and the dose adjusted accordingly.

📖 For more information, see Section G, Renal Insufficiency and End Stage Renal Disease in *Chapter VIII: Treatment in Special Situations.*

g. Use in hepatic disease

There are no precautions except for patients with alcohol-related hepatitis in whom there is an increased risk of seizures.

📖 For more information, see Section H, Hepatic Disease in *Chapter VIII: Treatment in Special Situations.*

h. Monitoring

Neuropsychiatric status should be assessed at least monthly and more frequently if symptoms develop. As noted above, measurements of serum concentrations may be necessary until an appropriate dose is established. For patients taking phenytoin, serum concentrations of phenytoin should be measured.

2. Ethionamide

Ethionamide is a second-line drug that is used for patients with drug-resistant tuberculosis disease caused by organisms that have demonstrated or presumed susceptibility to the drug.

a. Dose

ADULTS (maximum): 15-20 mg/kg **daily** (1.0 g/day), usually 500-750 mg/day in a single daily dose to facilitate DOT or 2 divided doses if necessary. The single daily dose may be better tolerated if given at bedtime or with food. There are no data to support intermittent dosing.

CHILDREN (maximum): 15-20 mg/kg **daily** (1.0 g/day).

b. Preparations and administration

Tablets (250 mg) for oral administration

c. Adverse reactions

Gastrointestinal effects: Ethionamide frequently causes gastrointestinal side effects, including a metallic taste, nausea, vomiting (often severe), loss of appetite, and abdominal pain. Symptoms may improve if doses are taken with food or at bedtime.

Hepatotoxicity: Ethionamide is similar in structure to INH and may cause similar side effects (see Chapter IV, Page 15). Hepatotoxicity occurs in about 2% of patients taking the drug.

Neurotoxicity: Peripheral neuritis, optic neuritis, anxiety, depression, and psychosis, has been reported in 1-2% of patients taking shorter courses of the drug with higher rates reported with prolonged treatment. Pyridoxine may be considered in the management of peripheral neuropathy.

Endocrine effects: Endocrine disturbances, including gynecomastia, alopecia, hypothyroidism, and impotence, have been described. Diabetes may be more difficult to manage in patients taking ethionamide.

d. Use in pregnancy and breastfeeding

Ethionamide crosses the placenta and is teratogenic in laboratory animals. **It should *not* be used in pregnancy.** There are no data on its safety for lactating women.

e. CNS penetration

CSF concentrations are equal to those in serum.

f. Use in renal disease

For patients having a creatinine clearance of less than 30 ml/minute or who are receiving hemodialysis, the dose should be reduced to 250-500 mg/day.

📖 For more information, see Section G, Renal Insufficiency and End Stage Renal Disease in *Chapter VIII: Treatment in Special Situations*.

g. Use in hepatic disease

Ethionamide should be used with caution in patients with underlying liver disease.

📖 For more information, see Section H, Hepatic Disease in *Chapter VIII: Treatment in Special Situations*.

h. Monitoring

Liver function tests should be obtained at baseline and, if there is underlying liver disease, at monthly intervals. The studies should be repeated if symptoms occur. Thyroid stimulating hormone should be measured at baseline and at 3 month intervals.

3. Streptomycin (SM), injectable

Streptomycin (SM) and EMB have been shown to be approximately equivalent when used in the initial phase of treatment with 6-month regimens. However, among patients likely to have acquired *M. tuberculosis* in countries with a high-burden of TB, the relatively high rate of resistance to SM limits its usefulness.

a. Dose

ADULTS (maximum): 15 mg/kg daily (1 g/day) parenterally, usually given as a single daily dose (5-7 days/week) initially, and then reducing to 2 - 3 times a week after the first 2-4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen. For persons 59 years of age or older, the dose should be reduced to 10 mg/kg per day (750 mg).

The dosing frequency should be reduced (i.e., 12-15 mg/kg per dose 2 – 3 times per week) in persons with renal insufficiency.

📖 For more information, see below, Use in Renal Disease.

CHILDREN (maximum): 20-40 mg/kg per day (1 g/day).

b. Preparations and administration

Streptomycin comes in an aqueous solution in vials of 1 gm for intramuscular (IM) injection <u>only</u>. Inject deep IM at a 90° angle into a large muscle mass. The preferred site for IM injection is the upper-outer quadrant of the buttock or the mid-lateral thigh. In children the mid-lateral thigh should be used. A normal well-developed adult can usually tolerate up to 3 ml of medication in one site. A smaller adult or child may only tolerate 2 ml or less per injection site. SM may also be administered intravenously (IV) over 30-60 minutes.

c. Adverse effects

<u>Ototoxicity:</u> The most important adverse reaction caused by SM is ototoxicity, including vestibular and hearing disturbances. The risk is increased with age or concomitant use of loop-inhibiting diuretics (furosemide, ethacrynic acid). The risk of ototoxicity increases with increasing single doses and with the cumulative dose, especially above 100-120 g.

Neurotoxicity: SM relatively commonly causes circumoral parasthesias immediately after injection. Rarely, it may interact with muscle relaxants to cause postoperative respiratory muscle weakness.

Nephrotoxicity: Occurs less commonly with SM than with amikacin, kanamycin, or capreomycin. Renal insufficiency requiring discontinuation occurs in about 2% of patients.

d. Use in pregnancy and breastfeeding

SM is contraindicated in pregnancy because of the risk of fetal hearing loss. It is compatible with breastfeeding.

e. CNS penetration

There is only slight diffusion of SM into CSF, even in patients with meningitis.

f. Use in renal disease

SM should be used with caution in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity. Because clearance is almost exclusively by the kidney, dosing adjustments are essential in patients with underlying renal insufficiency, including the elderly and those undergoing hemodialysis. In such patients, the dosing frequency should be reduced to 2 - 3 times weekly, but the milligram dose should be maintained at 12-15 mg/kg per dose to take advantage of the concentration-dependent bactericidal effect. Smaller doses may reduce the efficacy of this drug. The drug should be given after dialysis to facilitate Directly Observed Therapy (DOT) and to avoid premature removal of the drug. Serum drug concentrations should be monitored to avoid toxicity.

📖 For more information, see Section G, Renal Insufficiency and End Stage Renal Disease in *Chapter VIII: Treatment in Special Situations*.

g. Use in hepatic disease

No precautions are necessary.

📖 For more information, see section H., "Hepatic Disease" in *Chapter VIII: Treatment in Special Situations*.

h. Monitoring

All patients begun on SM should have a serum creatinine measurement done at baseline. For patients likely to be treated for more than 8 weeks, a serum creatinine measurement, audiogram, vestibular testing, and Romberg testing should be performed at baseline and repeated if there are symptoms of eighth nerve toxicity.

4. Amikacin and kanamycin, injectable

Amikacin and kanamycin are two closely related injectable second-line drugs that are used for patients with drug-resistant tuberculosis whose isolate has demonstrated or presumed susceptibility to the agents. There is nearly always complete cross-resistance between the two drugs, but most SM-resistant strains are susceptible to both. Amikacin rather than kanamycin is almost exclusively used in the U.S. as it may be more easily obtained, and serum drug concentration measurements are readily available.

a. Dose

ADULTS (maximum): 15 mg/kg daily (1.0 gm/day), intramuscular (IM) or intravenous (IV), usually given as a single daily dose (5-7 days/week) initially, and then reducing to 2 or 3 three times a week after the first 2-4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen. For persons 59 years of age or older the dose should be reduced to 10 mg/kg per day (750 mg).

The dosing frequency should be reduced (i.e., 12-15 mg/kg per dose, 2 or 3 times per week) in persons with renal insufficiency.

📖 For more information, see below, "Use in Renal Disease."

CHILDREN (maximum): 15-30 mg/kg daily (1 g/day) intramuscular (IM) or intravenous (IV) as a single dose.

b. Preparations and administration

Amikacin comes as an aqueous solution for intramuscular (IM) or intravenous (IV) injection in vials of 100 mg per 2 ml, 500 mg per 2 ml and 1 gm per 4 ml. Inject deep IM at a 90° angle into a large muscle mass; may be administered IV over 30-60 minutes. The preferred site for IM injection is the upper outer quadrant of the buttock or the mid-lateral thigh. In children the mid-lateral thigh should be used. A normal well-developed adult can usually tolerate up to 3 ml of medication in one site. A smaller adult or child may only tolerate 2 ml or less per injection site.

c. Adverse effects

<u>Ototoxicity:</u> Amikacin and kanamycin may cause deafness, but they cause less vestibular dysfunction than SM. Ototoxicity is more common with concurrent use of diuretics.

<u>Nephrotoxicity:</u> Amikacin and kanamycin may be more nephrotoxic than SM. Renal impairment was seen in a higher frequency in patients with initially increased creatinine levels, patients receiving larger total doses, and patients receiving other nephrotoxic agents.

d. Use in pregnancy and breastfeeding

Both amikacin and kanamycin are contraindicated in pregnant women because of risk of fetal nephrotoxicity and congenital hearing loss. Both amikacin and kanamycin are compatible with breastfeeding.

e. CNS penetration

Only low concentrations of the drugs are found in CSF, although slightly higher concentrations have been found in the presence of meningitis.

f. Use in renal disease

Amikacin and kanamycin should be used with caution in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity. Because clearance is almost exclusively by the kidney, dosing adjustments are essential in patients with underlying renal insufficiency, including the elderly and those receiving hemodialysis. In such patients, the dosing frequency should be reduced to 2 or 3 times per week, but the dose should be maintained at 12-15 mg/kg to take advantage of the concentration dependent bactericidal effect. Smaller doses may reduce the efficacy of this drug. The drug should be given after dialysis to facilitate Directly Observed Therapy (DOT) and to avoid premature removal of the drug. Serum drug concentrations should be monitored to avoid toxicity.

📖 For more information, see Section G, Renal Insufficiency and End Stage Renal Disease in *Chapter VIII: Treatment in Special Situations*.

g. Use in hepatic disease

No precautions are necessary.

📖 For more information, see Section H, Hepatic Disease in *Chapter VIII: Treatment in Special Situations*.

h. Monitoring

Monitoring should be done as described for SM.

5. Capreomycin, injectable

Capreomycin is a second-line injectable drug that is used for patients with drug-resistant tuberculosis caused by organisms that have known or presumed susceptibility to the drug.

a. Dose

ADULTS (maximum): 15 mg/kg per day (1.0 g/day), usually given as a single daily dose 5 to 7 times a week, and reduced to 2 or 3 times a week after the first 2-4

months or after culture conversion, depending on the efficacy of the other drugs in the regimen. For persons 59 years of age or older the dose should be reduced to 10 mg/kg per day (750 mg).

The dosing frequency should be reduced to 12-15 mg/kg 2 or 3 times per week in persons with renal insufficiency.

📖 For more information, see below, Use in Renal Disease.

CHILDREN (maximum): 15-30 mg/kg per day (1 g/day) as a single daily or twice weekly dose.

b. Preparations and administration

Capreomycin is available in vials of 1 g for both intramuscular and intravenous administration. Inject deep IM at a 90° angle into a large muscle mass; may be administered IV over 30-60 minutes. The preferred site for IM injection is the upper outer quadrant of the buttock or the mid-lateral thigh. In children the mid-lateral thigh should be used. A normal well-developed adult can usually tolerate up to 3 ml of medication in one site. A smaller adult or child may only tolerate 2 ml or less per injection site.

c. Adverse effects

Nephrotoxicity: Nephrotoxic effects may result in reduced creatinine clearance or potassium and magnesium depletion. Proteinuria is common. Significant renal toxicity requiring discontinuation of the drug has been reported to occur in 20-25% of patients.

Ototoxicity: Vestibular disturbances, tinnitus, and deafness appear to occur more often in elderly persons or those with preexisting renal impairment.

d. Use in pregnancy and breastfeeding

Capreomycin should be avoided in pregnancy because of risk of fetal nephrotoxicity and congenital hearing loss. It has also been known to cause wavy ribs in lab animals. There is insufficient evidence around the use of capreomycin with breastfeeding so it should be avoided.

e. CNS penetration

Capreomycin does not penetrate into the CSF.

f. Use in renal disease

Capreomycin should be used with caution in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity. Because capreomycin is nearly entirely cleared by the kidneys, dosing adjustments are

essential in patients with underlying renal insufficiency and end-stage renal disease, including patients undergoing hemodialysis. In such patients, the dosing frequency should be reduced to 2 or 3 times weekly, but the milligram dose should be maintained at 12-15 mg/kg per dose to take advantage of the concentration-dependent bactericidal effect. Smaller doses may reduce the efficacy of this drug. The drug should be given after dialysis to facilitate directly observed therapy (DOT) and avoid premature removal of the drug. Serum drug concentrations should be monitored to avoid toxicity.

📖 For more information, see Section G, Renal Insufficiency and End Stage Renal Disease in *Chapter VIII: Treatment in Special Situations*.

g. Use in hepatic disease

No precautions are necessary.

📖 For more information, see section H, Hepatic Disease in *Chapter VIII: Treatment in Special Situations*.

h. Monitoring

Monitoring should be performed as described for SM. In addition, serum potassium and magnesium concentrations should be measured at baseline and at least at monthly intervals.

6. P-Aminosalicylic acid (PAS)

P-Aminosalicylic acid (PAS) is an oral drug used in treatment of drug-resistant tuberculosis caused by organisms that are susceptible to the drug.

a. Dose

ADULTS: 8-12 g/day in 2 or 3 doses. For PAS granules, 4 g 3 times daily has been the usual dosage. However, it has been shown that administration of 4 g twice daily is adequate to achieve the target serum concentration. Once-daily directly observed therapy (DOT) dosing has been done with doses of 6-8 grams to avoid self administered doses.

CHILDREN: 200-300 mg/kg per day in 2 to 4 divided doses.

b. Preparations and administration

The only available formulation in the United States is granules in 4-g packets (Paser granules). Tablets (500 mg) are still available in some countries. A solution for intravenous administration is available in Europe.

c. Adverse effects

Hepatotoxicity: Hepatotoxicity in some patients has been attributed, at least in part, to PAS.

Gastrointestinal distress: This is the most common side effect of PAS. The incidence of gastrointestinal side effects is less with lower doses (8 g daily) and with the granular formulation of the drug.

Malabsorption syndrome: This is characterized by steatorrhea and low serum folate levels.

Hypothyroidism: This is a common side effect, especially with prolonged administration or concomitant use of ethionamide. It may be accompanied by goiter formation. Thyroid hormone replacement may be required. Thyroid function returns to normal after discontinuation of the drug.

Coagulopathy: A doubling of the prothrombin time that seemed to be lessened by co-administration of streptomycin has been reported.

d. Use in pregnancy and breastfeeding

It is not known if PAS crosses the placenta; however, PAS has been used safely in pregnancy. It is found in breast milk so should not be given to lactating women.

e. CNS penetration

The drug has marginal efficacy in meningitis.

f. Use in renal disease

Approximately 80% of the drug is excreted in the urine. Unless there is no alternative, PAS is contraindicated in severe renal insufficiency. The drug should be given after dialysis to facilitate directly observed therapy (DOT) and avoid premature removal of the drug.

📖 For more information, see section G, Renal Insufficiency and End Stage Renal Disease in *Chapter VIII: Treatment in Special Situations*.

g. Use in hepatic disease

The drug may be used in usual doses but with increased laboratory and clinical monitoring.

📖 For more information, see section H, Hepatic Disease in *Chapter VIII: Treatment in Special Situations*.

h. Monitoring

Hepatic enzymes and thyroid function should be measured at baseline. With prolonged therapy (more than 3 months), thyroid function should be checked every 3 months.

7. Fluoroquinolones

Of the fluoroquinolones, levofloxacin and moxifloxacin are believed to have the most efficacy against *M. tuberculosis*. On the basis of cumulative experience suggesting a good safety profile with long-term use of levofloxacin, this drug is the preferred oral drug for treating drug-resistant tuberculosis caused by organisms known or presumed to be sensitive to this class of drugs, or when first-line drugs cannot be used because of intolerance. Data on long-term safety and tolerability of moxifloxacin especially at doses above 400 mg/day is limited. Cross-resistance has been demonstrated among ciprofloxacin, ofloxacin, and levofloxacin and presumably is a class effect. Fluoroquinolones should not be considered first-line agents for the treatment of drug-susceptible tuberculosis except in patients who are intolerant of first-line drugs.

a. Dose

The doses given are for levofloxacin.

ADULTS: 500-1,000 mg, usually 750 mg daily.

CHILDREN: The long-term (more than several weeks) use of fluoroquinolones in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with multi-drug-resistant (MDR) tuberculosis. The optimal dose is not known.

b. Preparations and administration (levofloxacin)

Tablets (250 mg, 500 mg, 750 mg), aqueous solution (500 mg) for IV administration

c. Adverse effects (levofloxacin)

<u>Gastrointestinal disturbance:</u> Nausea and bloating occur in 0.5-1.8% of patients taking levofloxacin.

<u>Neurologic effects:</u> Dizziness, insomnia, tremulousness, and headache occur in 0.5% of patients.

<u>Cutaneous reactions:</u> Rash, pruritis, and photosensitivity occur in 0.2-0.4% of patients.

d. Use in pregnancy and breastfeeding

This class of drugs is may be safe in pregnancy but there are limited data and these drugs are in FDA Category C with a recommendation that they not be used in pregnant women. They do cross the placenta and there is has been little experience with long-term fluoroquinolone use during pregnancy. It is not known if they are safe for breastfeeding but are also in a FDA recommendation to avoid use during breast feeding. Risk and benefits must be weighed and discussed with patients with MDR TB who are at risk of fatal outcomes and ongoing transmission to family members.

e. CNS penetration

The concentration in CSF after administration of a standard dose of levofloxacin is 16-20% of that in serum.

f. Interference with absorption

Because antacids and other such medications markedly decrease absorption of fluoroquinolones, it is critical that any fluoroquinolone not be administered within 2 hours of such medications.

g. Use in renal disease

The drug is cleared primarily (80%) by the kidney. Dosage adjustment (750-1,000 mg 3 times a week) is recommended if creatinine clearance is less than 50 ml/minute. It is not cleared by hemodialysis. Supplemental doses after dialysis are not needed.

📖 For more information, see Section G, Renal Insufficiency and End Stage Renal Disease in *Chapter VIII: Treatment in Special Situations*.

h. Use in hepatic disease

Drug levels are not affected by hepatic disease. It is presumed to be safe for use in individuals with severe liver disease, but as with all drugs, should be used cautiously.

📖 For more information, see Section H, Hepatic Disease in *Chapter VIII: Treatment in Special Situations*.

i. Monitoring

No specific laboratory monitoring is recommended.

E. Drug Interactions

Interactions between drugs can result in changes in the concentrations of one or both of the drugs involved. There are relatively few interactions that substantially change the

concentrations of anti-tuberculosis drugs. Much more often, the anti-tuberculosis drugs cause clinically relevant changes in the concentrations of other drugs. The exceptions to this general rule are rifabutin and the fluoroquinolones.

1. Interactions Affecting Anti-tuberculosis Drugs

a. Rifabutin

Rifabutin is partially metabolized by the gene cytochrome P450 (CYP3A). Inhibitors of CYP3A increase serum concentrations of rifabutin and one of its metabolites, sometimes to toxic levels. For example, administration of ritonavir, a potent CYP3A inhibitor, with the standard daily dose of rifabutin increases the serum concentration of rifabutin fourfold. Conversely, administering rifabutin with a CYP3A inducer decreases its concentration, perhaps to ineffective levels. For example, efavirenz, an antiretroviral drug, decreases rifabutin serum concentrations by about one-third.

b. Fluoroquinolones

Absorption of the fluoroquinolones is markedly decreased by ingestion with medications containing divalent cations (calcium, iron, zinc), including:

- antacids
- supplements or vitamins containing calcium
- iron or zinc
- sucralfate (used to treat peptic ulcers)
- the chewable tablet formulation of didanosine (an NNRTI).

These drug interactions can be avoided by ensuring that medications containing divalent cations are ingested at least 2 hours apart from doses of fluoroquinolones.

2. Effects of Anti-Tuberculosis Drugs on Other Drugs

a. Drug interactions due to rifamycins

The drugs used to treat tuberculosis affect the metabolism of many other drugs and can result in a lack of efficacy or toxicity. Most of the clinically relevant interactions between drugs involving the anti-tuberculosis drugs are due to the effect of the rifamycins (rifampin, rifabutin, and rifapentine) on the metabolism of other drugs. All of the rifamycins are inducers of a variety of metabolic pathways, particularly those involving the various isozymes of the cytochrome P450 system. By inducing the activity of metabolic enzymes, rifamycin therapy results in a decrease in the serum concentration of many drugs, often below therapeutic levels. The rifamycins differ substantially in their potency as enzyme inducers. Rifampin is the most potent,

rifapentine is intermediate, and rifabutin is the least potent enzyme inducer. Some of these drug interactions can be managed with close clinical or laboratory monitoring and dose increases of the medication(s) affected by the rifamycins. If the dose of a medication is increased to compensate for the effect of a rifamycin, it is critical to remember to decrease the dose within 2 weeks after the rifamycin is discontinued.

In some situations, rifabutin can be used in place of rifampin, if there is an unacceptable drug interaction between rifampin and another drug, such as cyclosporine and most of the HIV-1 protease inhibitors. However, all the rifamycins may cause unacceptable decreases in the serum concentrations of certain drugs.

b. Drug interactions due to isoniazid (INH)

INH can increase concentrations of some drugs to the point of toxicity especially the anticonvulsants:

- Phenytoin (Dilantin)
- Carbamazepine (Tegretol).

INH may also increase the concentrations of benzodiazepines such as:

- Diazepam (Valium)
- Triazolam (Halcion)

Rifampin has the opposite effect on the serum concentration of many of these drugs. The combined effect of rifampin and INH is usually a decrease in the concentration of the drugs such as phenytoin and diazepam.

INH may increase toxicity of the following drugs, but these potential interactions have not been well studied:

- Acetaminophen (Tylenol)
- Valproate (Depakote)
- Serotonergic antidepressants (e.g. Paxil, Prozac, Zoloft, Zyprexa, Geodon)
- Warfarin (Coumadin)
- Theophylline
- Disulfiram (Antabuse).

c. Drug interactions due to fluoroquinolones

Ciprofloxacin inhibits the metabolism of theophylline and can cause toxicity. However, levofloxacin, gatifloxacin, and moxifloxacin do not affect theophylline metabolism.

F. Pregnancy and Breastfeeding

Because of the risk of tuberculosis to the fetus, treatment of tuberculosis in pregnant women should be initiated whenever the probability of maternal disease is moderate to high. The initial treatment regimen should consist of INH, RIF, and EMB. Although all of these drugs cross the placenta, they do not appear to have teratogenic effects. Streptomycin is the only anti-tuberculosis drug documented to have harmful effects on the human fetus (congenital deafness) and should not be used. Although PZA is recommended for routine use in pregnant women by the WHO and the IUATLD, the drug has not been routinely used in the United States because of insufficient data to determine safety. However, some public health jurisdictions in the United States have used PZA in pregnant women with no reported adverse events. If PZA is not included in the initial treatment regimen, the minimum duration of therapy is 9 months.

Breastfeeding should not be discouraged for women being treated with the first-line anti-tuberculosis agents because the small concentrations of these drugs in breast milk do not produce toxicity in the nursing newborn. Conversely, drugs in breast milk should not be considered to serve as effective treatment for tuberculosis or for latent tuberculosis infection in a nursing infant. Pyridoxine (Vitamin B_6) supplementation (25 mg/day) is recommended for all women taking INH who are either pregnant or breastfeeding. The amount of pyridoxine (Vitamin B_6) in multivitamins is variable but generally less than the needed amount.

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