NPTC Drug Class Review: Antituberculous Drugs

Introduction

Tuberculosis (TB) is an infectious disease caused by the microorganism *Mycobacterium tuberculosis*. TB occurs worldwide, with greater frequency in less developed countries. More than 2 billion of the world's population is infected (including 11 million in the US). Nearly 9 million of these develop active TB each year. Each of these will infect 10-15 others. Approximately 5% of these cases involve multidrug-resistant (MDR) TB (cases that are at least resistant to isoniazid and rifampin). Extensively drug-resistant (XDR) tuberculosis has been emerging over the past several years (defined as MDR TB that is also resistant to flouroquinolones and at least one of the three injectable second-line agents: amikacin, kanamycin, or capreomycin) and has been identified in at least 49 countries worldwide. Approximately 2 million TB deaths occur annually worldwide. For many years, TB in the United States was declining at a steady rate. In the 1980's there was an unprecedented resurgence in the US, primarily in groups that have a high prevalence of HIV infection and foreign-born peoples. TB incidence is higher in the poor, homeless and the foreign born. It is also higher in males than females, and higher in cities when compared to rural areas. In 2008 in the United States, the incidence of clinical disease was 4.2 cases per 100,000 population.

Transmission

TB is spread through exposure to the TB bacilli in airborne droplet nuclei produced when an individual with infectious pulmonary or laryngeal TB coughs, sneezes, talks, etc. Droplet nuclei (approximately 1-5 microns in size) are discharged into the environment during respiratory efforts such as coughing, speaking, singing or sneezing. Infection occurs when a susceptible individual inhales droplet nuclei containing the TB bacillus. Prolonged close contact to an infectious person may result in infection of contacts. Once in the lung, the organisms can be spread throughout the body. Usually in 2-10 weeks after initial infection, the immune response of the individual limits further spread of the organism. The primary reservoir for TB is man. However, rarely cattle, primates, and other animals may be infected. Although TB is an airborne infectious disease, it is not as contagious as other airborne illnesses such as colds, chickenpox or measles.

The incubation period from infection to the time when a TB skin test shows a positive reaction is usually 4-12 weeks. Overall, approximately 5-10% of individuals that have positive TB tests may develop active TB over their lifetime. The risk for developing active disease is greater during the first two years after infection.

Theoretically, the period of communicability of TB is as long as viable organisms are being discharged in the sputum. Inadequately or poorly treated individuals can remain communicable for years. Factors affecting communicability include the number of organisms released into the environment, the virulence of the organism, ventilation or concentration of organisms in the environment.

Signs and Symptoms of Tuberculosis

Symptoms of TB may include chronic cough, productive cough, bloody sputum, weakness, weight loss, fatigue, loss of appetite, and night sweats. Most TB is located in the lungs and is called pulmonary TB. However, TB infection can occur in other locations in the body.

Persons with immunocompromising conditions have a greater risk for the progression to active disease after infection. HIV is the strongest known risk factor yet identified for the progression from latent TB infection to active disease.

Groups with an Increased Prevalence of Tuberculosis

Groups known to have a higher prevalence of TB infection include medically underserved populations (including some African Americans, Hispanics, Asians and Pacific Islanders, Native Americans and Alaskan Natives). Homeless persons, current and past prison inmates, alcoholics, IV drug users, and the elderly also have a higher prevalence of TB than the general population.

Groups with a higher risk of progression from latent TB infection to active TB disease include persons with certain medical conditions including HIV infection, silicosis, diabetes, a history of certain abdominal surgeries and being 10% or more below normal body weight.

Treatment of Tuberculosis

Diagnostic measures for identifying TB include history, physical exam, Purified Protein Derivative (PPD) skin test, interferon-gamma release assays, chest x-ray, and microscopic examination of sputum and cultures. Other methods such as bronchoscopy and biopsy are also used. TB may be difficult to diagnose in patients with HIV infection or other immunocompromising conditions. Patients with active TB should be in isolation in the hospital or at home until sputum and culture results are negative.

A positive TB test (PPD) indicates infection with the TB bacteria, but does not in itself mean that an individual has active TB disease. Individuals with a positive PPD that do not have any other signs or symptoms and have a negative chest x-ray are not considered to have active TB.

Patients with active TB are given a combination of specific medications for at least 6 months. A combination of medications is given to prevent drug resistance.

Individuals with latent TB infection (positive PPD test and no signs or symptoms of disease) may be put on preventive medication for 9 months. Individuals with latent TB infection are not contagious and can continue to work and carry on normal activities.

Impact of Tuberculosis on Native Americans/Alaska Natives

Native Americans/Alaska Natives accounted for 1.0 percent of TB cases in 2005. Since 1993, the TB case rate in American Indians has decreased by 50.4 percent. However, the TB case rate is over five times greater in American Indians/Alaska Natives (6.9 per 100,000) than in non-Hispanic Whites (1.3 per 100,000). Alaska and Oklahoma saw the greatest number of TB cases among American Indians/Alaska Natives in 2005. However, in North Dakota and Montana, half of the TB cases reported were in persons of American Indian/Alaska Native heritage.

Antituberculous Drugs

The purpose of this review is to support the IHS National P&T Committee in making recommendations for the IHS National Core Formulary (NCF) regarding the inclusion of antituberculous drugs. For the purpose of this review, we will include only the following first-line agents as outlined in Table 1.

Table 1: Antituberculous drugs

		Adult dosing				Pediatric dosing	
Drug	**Preparations**	**Daily (max)**	**Once weekly (max)**	**Twice weekly (max)**	**Thrice weekly (max)**	**Daily (max)**	**Twice weekly (max)**
Isoniazid (INH)	Tablets: 50 mg, 100 mg, 300 mg Syrup: 50 mg/5ml Aqueous soln: 100 mg/ml	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	10-15 mg/kg (300 mg)	20-30 mg/kg (900 mg)
Rifampin (RIF)	Capsules: 150 mg, 300 mg	10 mg/kg (600 mg)		10 mg/kg (600 mg)	10 mg/kg (600 mg)	10-20 mg/kg (600 mg)	10-20 mg/kg (600 mg)
Pyrazinamide (PZA)	Tablets: 500 mg (scored)	See Table 2		See Table 2	See Table 2	15-30 mg/kg (2 gm)	50 mg/kg (2 gm)
Ethambutol (EMB)	Tablets: 100 mg, 400 mg	See Table 3		See Table 3	See Table 3	15-20 mg/kg (1 gm)	50 mg/kg (2.5 gm)
Rifapentine (RFT)	Tablets: 100 mg (film-coated)		10 mg/kg (600 mg)				
Rifabutin	Capsules: 150 mg	5 mg/kg (300 mg)		5 mg/kg (300 mg)	5 mg/kg (300 mg)		
INH + RIF (Rifamate®)	Capsule: INH 150 mg + RIF 300 mg	2 capsules					

INH + RIF + PZA (Rifater®)	Tablet: INH 50 mg + RIF 120 mg + PZA 300 mg	≤ 44 kg: 4 tabs 45-54 kg: 5 tabs ≥ 55 kg: 6 tabs					

Table 2: Suggested pyrazinamide doses, using whole tablets, for adults 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

Table 3: Suggested ethambutol doses, using whole tablets, for adults 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

Table 4: Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms

Initial phase			Continuation phase			Range of total doses (minimal duration)	Rating* (evidence)†	
Regimen	**Drugs**	**Interval and doses‡ (minimal duration)**	**Regimen**	**Drugs**	**Interval and doses‡§ (minimal duration)**		**HIV–**	**HIV+**
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	1a	INH/RIF	Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)¶	182–130 (26 wk)	A (I)	A (II)
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A (I)	A II)#
			1c**	INH/RPT	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk),¶ then twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses 18 wk)	62–58 (26 wk)	A (II)	B (II)#
			2b**	INH/RPT	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	4a	INH/RIF	Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)¶	273–195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

Definition of abbreviations: EMB = Ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine.
* Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.
† Definition of evidence ratings: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.
‡ When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.
§ Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.
¶ Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is AIII.
# Not recommended for HIV-infected patients with CD4+ cell counts <100 cells/µl.
** Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

Table 5: Revised drug regimens for treatment of latent tuberculosis infection (LTBI) in adults*

			Rating§ (Evidence)¶	
Drugs	**Interval and duration**	**Comments†**	**HIV -**	**HIV +**
Isoniazid	Daily for 9 months**††	In HIV-infected persons, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs).	A (II)	A (II)
	Twice weekly for 9 months**††	Directly observed therapy (DOT) must be used with twice-weekly dosing.	B (II)	B (II)
Isoniazid	Daily for 6 months††	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiograph, or children.	B (I)	C (I)
	Twice weekly for 6 months††	DOT must be used with twice-weekly dosing.	B (II)	C (I)

Rifampin[§§]	Daily for 4 months	Used for persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB. In HIV-Infected persons, most protease inhibitors or delaviridine should not be administered concurrently with Rifampin. Rifabutin with appropriate dose adjustments can be used with protease inhibitors (saquinivir should be augmented with ritonavir) and NNRTIs (except delaviridine). Clinicians should consult web-based updates for the latest specific recommendations.	B (II)	B (III)
Rifampin plus pyrazinamide (RZ)	Daily for 2 months	RZ generally should not be offered for treatment of LTBI for HIV-infected or HIV-negative persons	D (II)	D (III)
	Twice weekly for 2-3 months		D (II)	D (III)

* Adapted from CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000; 49(No. RR-6).
† Interactions with human immunodeficiency virus (HIV)-related drugs are updated frequently and are available at http://www.aidsinfo.nih.gov/guidelines.
§ Strength of the recommendation:
- A. Both strong evidence of efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
- B. Moderate evidence for efficacy or strong evidence for efficacy but only limited clinical benefit supports recommendation for use. Should generally be offered.
- C. Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment or alternative approaches. Optional.
- D. Moderate evidence for lack of efficacy or for adverse outcome support a recommendation against use. Should never be offered.
- E. Good evidence for lack of efficacy or for adverse outcome support a recommendation against use. Should never be offered.

¶ Quality of evidence supporting the recommendation:
- I. Evidence from at least one properly andomized controlled trial.
- II. Evidence from at least one well-designed clinical trail without randomization from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results from uncontrolled experiments.
- III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

** Recommended regimen for persons aged <18 years.
†† Recommended regimens for pregnant women.
§§ The substitution of rifapentine for Rifampin is not recommended because rifapentine's safety and effectiveness have not been established for patients with LTBI.

Isoniazid

Role in treatment regimen: Isoniazid (INH) is a first-line agent for treatment of all forms of tuberculosis caused by organisms known or presumed to be susceptible to the drug. It has profound early bactericidal activity against rapidly dividing cells.

Adverse effects:
Asymptomatic elevation of aminotransferases: Aminotransferase elevations up to five 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: (see Table 6.) Data indicate that the incidence of clinical hepatitis is lower than was previously thought. Hepatitis occurred in only 0.1–0.15% of 11,141 persons receiving INH alone as treatment for latent tuberculosis infection in an urban tuberculosis control program. Prior studies suggested a higher rate, and a meta-analysis of six studies estimated the rate of clinical hepatitis in patients given INH alone to be 0.6%. In the meta-analysis the rate of clinical hepatitis was 1.6% when INH was given with other agents, not including RIF. The risk was higher when the drug was combined with RIF, an average of 2.7% in 19 reports. For INH alone the risk increases with increasing age; it is uncommon in persons less than 20 years of age but is nearly 2% in persons aged 50–64 years. The risk also may be increased in persons with underlying liver disease, in those with a history of heavy alcohol consumption, and, data suggest, in the postpartum period, particularly among Hispanic women.

Table 6: Clinical hepatitis in persons taking isoniazid and rifampin*

Drug	Number of studies	Patients	Clinical Hepatitis (%)
INH	6	38,257	0.6
INH plus other drugs but not RIF	10	2,053	1.6
INH plus RIF	19	6,155	2.7
RIF plus other drugs but not INH	5	1,264	1.1

Definition of abbreviations: INH = Isoniazid; RIF = rifampin.
* **Source:** Steele MA, Burk RF, Des Prez RM. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. *Chest 1991*;99:465–471.

Fatal hepatitis: A large survey estimated the rate of fatal hepatitis to be 0.023%, but more recent studies suggest the rate is substantially lower. The risk may be increased in women. Death has been associated with continued administration of INH despite 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 increased in persons with other conditions that may be associated with neuropathy such as nutritional deficiency, diabetes, HIV infection, renal failure, and alcoholism, as well as for pregnant and breastfeeding women. Pyridoxine supplementation (25 mg/day) is recommended for patients with these conditions to help prevent this neuropathy.

Central nervous system effects: Effects such as dysarthria, irritability, seizures, dysphoria, and 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, necessitating drug discontinuation.

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

Monoamine (histamine/tyramine) poisoning: This has been reported to occur after ingestion of foods and beverages with high monoamine content but 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: Use of the commercial liquid preparation of INH, because it contains sorbitol, is associated with diarrhea.

Use in pregnancy: INH is considered safe in pregnancy, but the risk of hepatitis may be increased in the peripartum period. Pyridoxine supplementation (25 mg/day) is recommended if INH is administered 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.

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

Use in renal disease: INH can be used safely without dose adjustment in patients with renal insufficiency and with end-stage renal disease who require chronic hemodialysis.

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.

Monitoring: Routine monitoring is not necessary. However, for patients who have preexisting liver disease or who develop abnormal liver function that does not require discontinuation of the drug, liver function tests should be measured monthly and when symptoms occur. 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.

Rifampin

Role in treatment regimen: Rifampin (RIF) is a first-line agent 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 semidormant bacterial populations, thus accounting for its sterilizing activity. Rifampin is an essential component of all short-course regimens.

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, occurring in 0.07–0.3% of patients.

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

Flulike syndrome: This may occur in 0.4–0.7% of patients receiving 600 mg twice weekly but not with daily administration of the same dose. Symptoms are more likely to occur with intermittent administration of a higher dose.

Hepatotoxicity: Transient asymptomatic hyperbilirubinemia may occur in as many as 0.6% of patients receiving the drug. More severe clinical hepatitis that, typically, has a cholestatic pattern may also occur. 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 flulike syndrome, other reactions thought to be immune mediated include the following: 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, and warfarin. In addition there are important bidirectional interactions between rifamycins and antiretroviral agents.

Use in pregnancy: RIF is considered safe in pregnancy.

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.

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

Use in hepatic disease: Clearance of the drug 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.

Monitoring: No routine monitoring tests are required. However, rifampin causes many drug interactions, which may necessitate regular measurements of the serum concentrations of the drugs in question.

Rifabutin

Role in treatment regimen: Rifabutin is used as a substitute for RIF in the treatment of all forms of tuberculosis caused by organisms that are known or presumed to be susceptible to this agent. The drug is generally reserved for patients who are receiving any medication having unacceptable interactions with rifampin or have experienced intolerance to rifampin.

Adverse effects:
Hematologic toxicity: In a placebo-controlled, double-blind trial involving patients with advanced acquired immunodeficiency syndrome (AIDS) (CD4+ cell counts <200 cells/µl), neutropenia occurred in 25% compared with 20% in patients receiving placebo ($p = 0.03$). Neutropenia severe enough to necessitate discontinuation of the drug occurred in 2% of patients receiving the drug. The effect 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 (less than 0.01%) complication when the drug is given alone at a standard (300 mg daily) dose. The occurrence is higher (8%) with higher doses or when rifabutin is used in combination with macrolide antimicrobial agents that reduce its clearance. Uveitis may also occur with other drugs that reduce clearance such as protease inhibitors and azole antifungal agents.

Gastrointestinal symptoms: These 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 occurred in 1–2% of persons receiving a standard 300-mg dose. It is more common at higher doses. Polyarthralgias have not been noted in more recent studies involving both HIV-infected and uninfected patients.

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: Although initially reported to occur in as many as 4% of patients with advanced HIV infection, subsequent studies suggest that rash is only rarely (less than 0.1%) associated with rifabutin.

Flulike syndrome: Flulike syndrome is rare (less than 0.1%) 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.

Use in pregnancy: There are insufficient data to recommend the use of rifabutin in pregnant women; thus, the drug should be used with caution in pregnancy.

CNS penetration: The drug penetrates inflamed meninges.

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

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.

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.

Rifapentine

Role in treatment regimen: Rifapentine may be used once weekly with INH in the continuation phase of treatment for HIV-seronegative patients with noncavitary, drug-susceptible pulmonary tuberculosis who have negative sputum smears at completion of the initial phase of treatment.

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

Use in pregnancy: There is not sufficient information to recommend the use of rifapentine for pregnant women.

CNS penetration: There are no data on CSF concentrations of rifapentine.

Use in renal disease: The pharmacokinetics of rifapentine have not been evaluated in patients with renal impairment. Although only about 17% of an administered dose is excreted via the kidneys, the clinical significance of impaired renal function in the disposition of rifapentine is not known.

Use in hepatic disease: The pharmacokinetics of rifapentine and its 25-desacetyl metabolite were similar among patients with various degrees of hepatic impairment and not different from those in healthy volunteers, even though the elimination of these compounds is primarily via the liver. The clinical significance of impaired hepatic function in the disposition of rifapentine and its 25-desacetyl metabolite is not known.

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

Pyrazinamide

Role in treatment regimen: Pyrazinamide (PZA) is a first-line agent 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.

Adverse effects:
Hepatotoxicity: Early studies using doses of 40–70 mg/kg per day reported high rates of hepatotoxicity. However, in treatment trials with multiple other drugs, including INH, liver toxicity has been rare at doses of 25 mg/kg per day or less. In one study, however, hepatotoxicity attributable to PZA used in standard doses occurred at a rate of about 1%.

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

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 non-steroidal anti-inflammatory agents. In clinical trials of PZA in the initial intensive phase of treatment, arthralgias were not noted to be a significant problem.

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.

Use in pregnancy: There is little information about the safety of PZA in pregnancy. However, when there are sound reasons to utilize a 6-month course of treatment, the benefits of PZA may outweigh the possible (but unquantified) risk. The WHO and the IUATLD recommend this drug for use in pregnant women with tuberculosis.

CNS penetration: The drug passes freely into the CSF, achieving concentrations equivalent to those in serum.

Use in renal disease: PZA is cleared primarily by the liver, but its metabolites are excreted in the urine and may accumulate in patients with renal insufficiency. The dose may, therefore, need to be reduced in patients with renal insufficiency. It should be administered at a reduced dose (25–35 mg/kg) three times a week after dialysis in patients with end-stage renal disease. The risk of hyperuricemia caused by PZA is increased in patients with renal insufficiency.

Use in hepatic disease: Although the frequency is slightly lower than with INH or RIF, the drug 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.

Monitoring: Serum uric acid measurements are not recommended as a routine but may serve as a surrogate marker for compliance. Liver chemistry monitoring should be performed when the drug is used in patients with underlying liver disease or when it is used with rifampin in treating latent tuberculosis infection.

Ethambutol

Role in treatment regimen: 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 RIF resistance when primary resistance to INH may be present. Ethambutol is generally not recommended for routine use in children whose visual acuity cannot be monitored. However, if a child has adult-type tuberculosis or disease that is suspected or proven to be caused by organisms that are resistant to either INH or RIF, EMB should be used.

Adverse effects:
Retrobulbar neuritis: This is manifested as decreased visual acuity or decreased red-green color discrimination that may affect one or both eyes. The effect is dose related, with minimal risk at a daily dose of 15 mg/kg. No difference was found in the prevalence of decreased visual acuity between regimens that contained EMB at 15 mg/kg and those not containing the drug. The risk of optic toxicity is higher at higher doses given daily (18% of patients receiving more than 30 mg/kg per day) 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 occur in 0.2–0.7% of patients.

Use in pregnancy: EMB is considered safe for use in pregnancy.

CNS penetration: The agent penetrates the meninges in the presence of inflammation but does not have demonstrated efficacy in tuberculous meningitis.

Use in renal disease: EMB is cleared primarily 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 DOT after dialysis in patients with end-stage renal disease.

Use in hepatic disease: EMB can be used safely in patients with hepatic disease.

Monitoring: Patients should have baseline visual acuity testing (Snellen chart) and testing of color discrimination (Ishihara tests). At each monthly visit patients should be questioned regarding possible visual disturbances including blurred vision or scotomata. Monthly testing of visual acuity and color discrimination is recommended for patients taking doses greater than 15–25 mg/kg, patients receiving the drug for longer than 2 months, and any patient with renal insufficiency. Patients should be instructed to contact their physician or public health clinic immediately if they experience a change in vision. EMB should be discontinued immediately and permanently if there are any signs of visual toxicity.

Fixed-dose combination preparations

Role in treatment regimen: Two combined preparations, INH and RIF (Rifamate®) and INH, RIF, and PZA (Rifater®), are available in the United States. These formulations are a means of minimizing inadvertent monotherapy, particularly when DOT is not possible, and, therefore, may decrease the risk of acquired drug resistance. The use of fixed-dose formulations may reduce the number of pills that must be taken daily. Constituent drugs are combined in proportions compatible with daily treatment regimens. Formulations for intermittent administration are not available in the United States.

Adverse effects: See comments under individual drugs above.

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

CNS penetration: See comments under individual drugs above.

Use in renal disease: Rifamate® may be used in persons with renal insufficiency. Rifater® should not be used because of the potential need for adjustment of the dose of PZA.

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.

Conclusions

Tuberculosis continues to have a significant impact as a leading cause of death worldwide. Although disease rates are considerably lower in the U.S., Native Americans/Alaskan Natives (NA/AN) continue to see rates that are higher than the US average. Through constant vigilance, the use of effective medication regimens, and the application of Directly Observed Therapy (DOT) the rate of TB in NA/AN has decreased considerably in the past decade.

The first line antituberculous drugs, isoniazid, rifampin, pyrazinamide, ethambutol, rifapentine, and rifabutin, remain effect in the treatment of drug-sensitive tuberculosis. There role is more limited in management of MDR and XDR TB. NA/AN with either latent TB infection or active tuberculosis need access to effective treatments to further stem the spread of this potentially deadly disease. Consistent availability of these agents at all I/T/U facilities is important in preventing interruption of therapy in patients that travel during the course of their therapy. The use of fixed-dose products may play a role in improving adherence to these regimens and reduce the risk of the development of secondary resistance.

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