Mayo Clinic Proceedings

Published since 1926

VOLUME 67 FEBRUARY 1992 NUMBER 2

MAYO FOUNDATION
Room 660 Siebens Building
200 First Street Southwest
Rochester, MN 55905 U.S.A.

Address correction requested

ISSN 0025-6196

MACPAJ 67(2)105-210(1992)

mayo

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Antituberculous Agents

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Antituberculous agents have radically improved the prognosis of patients with active tuberculosis. Generally, 6-month and 9-month antituberculous regimens have been successful, and surgical therapy is rarely needed. Extrapulmonary tuberculosis should be managed with the same drug regimens as pulmonary tuberculosis. The major cause of therapeutic failure is poor compliance of the patient in taking the prescribed medication regularly. A second cause of failure of treatment is resistance of tubercle bacilli to antimicrobial agents used. When failure of treatment is apparent, careful reassessment by physicians experienced in the treatment of tuberculosis is indicated. A single drug should never be added to a failing regimen. Isoniazid administered prophylactically for 6 to 12 months is effective in most cases.

In the past 4 decades, antituberculous agents have radically improved the prognosis of patients with active tuberculosis. Most patients with tuberculosis can be cured with chemotherapy; surgical therapy is rarely necessary. In most cases, patients can be treated at home and can return to work soon after treatment has been initiated.

In this article, we discuss five antituberculous drugs—isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide. A few comments are offered about the quinolones, including ciprofloxacin. Discussion of other drugs such as cycloserine, ethionamide, *p*-aminosalicylic acid recrystallized in vitamin C, thiacetazone, capreomycin, and aminoglycosides other than streptomycin is beyond the scope of this article. Clofazimine, ansamycin, and some β-lactam antimicrobial agents with or without β-lactamase inhibitors either have antituberculous activity or are being investigated for such activity.

GENERAL COMMENTS

In the United States, conditions are suitable not only for a major increase in the morbidity and mortality from tuberculosis but also for the spread of resistant tuberculosis. This situation is particularly tragic because this disease is generally preventable and is certainly treatable. Since 1984, the expected continued decline in tuberculosis-associated morbidity has not occurred; in fact, in 1986 the morbidity began to increase.[1] Apparently, infections due to human immunodeficiency virus (HIV) are primarily responsible.[1]

HIV infection seriously impairs host defenses, especially the delayed-type hypersensitivity defenses necessary for combating tuberculosis. HIV is infecting those who abuse intravenously administered drugs, who are often noncompliant with therapeutic regimens. The result may be not only more treatment failures but also more cases with resistant organisms. Infected persons who are not taking medication are more likely to spread infection to others than are those who receive consistent treatment.

In 1989, an estimated 10 million persons in the United States were already infected with *Mycobacterium tuberculosis* (positive reactors to purified protein derivative). Approximately 21,000 new active clinical cases of tuberculosis arose from those 10 million. In addition, approximately 20,000 persons became newly infected with the organism, from which about 2,500 new active clinical cases arose.[2]

Certain specific 6-month and 9-month treatment regimens have been successful. In general, extrapulmonary tuberculosis should be managed with the drug regimens outlined for pulmonary tuberculosis. The major cause of therapeutic failure is poor compliance of the patient in taking

Individual reprints of this article are not available. The entire Symposium on Antimicrobial Agents will be available for purchase as a bound booklet from the *Proceedings* Circulation Office at a later date.

the prescribed medication regularly. Most state and county health departments have nurses and community-outreach services that will provide free medication and will help in supervision of therapy; thus, compliance can be improved. Thorough investigation and follow-up of contacts by health departments are essential for control of tuberculosis. Physicians and the health department must have an efficient, cooperative working relationship.

A second cause of therapeutic failure is resistance of tubercle bacilli to the antimicrobial agents used. When failure of treatment is apparent, careful reassessment by a physician experienced in the treatment of tuberculosis is indicated. A single drug should never be added to a failing regimen.

Family physicians, internists, and general hospital personnel have assumed increased responsibility for the diagnosis, isolation, treatment, and, particularly, follow-up surveillance of patients with tuberculosis. Nevertheless, problems have arisen, including misdiagnosis; poor communication among the hospital staff, the patient's physician, and the state and county health departments; and inadequate identification and investigation of persons exposed to the disease through contact with the patient.[3]

Khan and associates[4] described the atypical and the typical chest roentgenographic features in newly diagnosed cases of tuberculosis in adults. These findings may include pleural effusion, hilar adenopathy, and infiltrates of the lower lobe, as well as more typical manifestations in adults. Atypical manifestations in patients with acquired immunodeficiency syndrome (AIDS) are common.[5,6]

Isoniazid, administered prophylactically for 6 to 12 months, is effective in most cases. Rifampin, 600 mg/day for 1 year, is recommended for close contacts of those with isoniazid-resistant organisms.

The Centers for Disease Control and the American Thoracic Society have prepared an excellent document entitled "Core Curriculum on Tuberculosis."[2] Most of the treatment recommendations in the current article are based on that document. Several other publications also provide useful information on the treatment of tuberculosis.[7-9]

ISONIAZID

Isoniazid, also referred to as INH (isonicotinic acid hydrazide), is an almost perfect chemotherapeutic agent. It is bactericidal, inexpensive, and well absorbed when administered orally or parenterally. After several years of clinical experience with isoniazid, investigators noted that severe hepatotoxicity developed in a small percentage of patients.

Mode of Action and Main Pharmacologic Properties.—Isoniazid is a white, water-soluble, crystalline substance. It acts primarily by inhibiting the synthesis of mycolic acid, an important component of cell walls.[9,10]

Peak blood concentrations of isoniazid occur 1 to 2 hours after oral administration. The drug is widely distributed in the body—variable quantities are found in the pleural fluid, ascitic fluid, cerebrospinal fluid, caseous material, saliva, skin, and muscle.

Isoniazid is acetylated by the liver and excreted as a metabolite by the kidneys; it appears unchanged in the urine. Other metabolites, including hydrazones, are excreted in the urine as well. The relative fractions of isoniazid, acetylisoniazid, and hydrazones in the urine vary considerably among patients.

The duration of tuberculocidal blood levels depends on the rate of acetylation of isoniazid in the liver, which is genetically controlled. Among American and northern European populations, 45 to 65% demonstrate slow inactivation; Eskimos and Orientals are more likely to have rapid inactivation. Rapid acetylation is an autosomal dominant trait. Both patients with slow and those with rapid inactivation respond well clinically to standard doses of isoniazid. Those patients with slow acetylation may be more susceptible to toxic side effects related to higher blood levels (for example, peripheral neuritis), whereas those with rapid acetylation have a higher frequency of hepatotoxicity.

Investigators have suggested that the amount of activity of the liver enzyme cytochrome P-450 may also be related to isoniazid-induced hepatotoxicity. Results of experimental studies in animals suggest that single large doses of isoniazid saturate acetyltransferase and result in lower production of acetylhydrazine than that which occurs after administration of multiple small doses. The acetylhydrazine pathway seems to be related to hepatotoxicity.[11] Therefore, studies of the frequency of hepatotoxicity associated with thrice-weekly administration in comparison with daily isoniazid therapy seems important.[12] One study of patients taking isoniazid and rifampin revealed hepatotoxicity in 5% of those given a daily regimen and in 0 to 1% of those given a thrice-weekly regimen.[13]

Spectrum of Activity.—Most strains of *M. tuberculosis* are sensitive to isoniazid, whereas almost all strains of *M. avium* and *M. marinum* are resistant. Most strains of *M. kansasii* are sensitive to the drug but at higher concentrations than those effective for *M. tuberculosis*.

Adverse Effects.—Hepatitis is the most severe side effect associated with the use of isoniazid. It may be caused by conversion of isoniazid to acetylhydrazine or related hepatotoxic derivatives. The frequency of occurrence of hepatitis increases with advancing age (Table 1), in patients who also take rifampin, and in those who consume alcohol daily. Because of the association between age and the occurrence of hepatitis, isoniazid prophylaxis is recommended most frequently for patients younger than 35 years of age.

Table 1.—**Effect of Age on the Occurrence of Hepatitis in Patients Taking Isoniazid**

Age (yr)	Frequency (%)
<20	Rare
20-34	≤0.3
35-49	≤1.2
≥50	≤2.3

Data from the Tuberculosis Advisory Committee report.[14]
From Van Scoy RE, Wilkowske CJ: Antituberculous agents: isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide. Mayo Clin Proc 58:233-240, 1983

Patients taking isoniazid should be advised about the symptoms of hepatitis. They should discontinue use of the drug and consult their physicians immediately if such symptoms are noted. Furthermore, some mechanism should be established for monthly communication with the physician or health-care worker, regardless of whether monthly determinations of serum glutamic-oxaloacetic or glutamic-pyruvic transaminase are obtained. Mild increases in serum transaminase concentrations will develop in 10% or more of patients who receive isoniazid, but the levels seldom exceed 2 to 3 times the normal upper limits.[15] Most physicians recommend continuation of isoniazid therapy unless transaminase values exceed 3 to 5 times the normal levels. Some physicians might advise discontinuation of isoniazid prophylaxis if serum transaminase concentrations are 3 times the normal level.

Daily consumption of alcohol may increase the metabolism of isoniazid and thereby both increase the risk of hepatotoxicity and decrease the therapeutic effect of the drug. Aluminum-containing antacids may interfere with the absorption of isoniazid. Moreover, isoniazid may increase the blood levels of and the toxicity from phenytoin (Dilantin). Concurrent administration of disulfiram (Antabuse) and isoniazid may cause psychotic episodes as a result of altered metabolism of dopamine.[16] Severe acetaminophen-associated toxicity may occur when large doses are taken by a patient who is also receiving isoniazid.[17]

Isoniazid causes increased urinary excretion of pyridoxine (vitamin B_6) and may produce symptoms of pellagra, such as rash, peripheral neuritis, and anemia. This side effect is particularly prevalent with use of large doses (more than 300 mg/day) in nutritionally deficient persons such as alcoholics. In such cases, 10 to 50 mg of pyridoxine per day is recommended. Pyridoxine may also prevent other toxic reactions in the central nervous system.

As with any drug, the use of isoniazid may be associated with the occurrence of rash, urticaria, fever, and other hypersensitivity reactions. Various other side effects have been noted, including seizures, optic neuritis, psychotic reactions, arthralgias, vasculitis, shoulder-hand syndrome, and agranulocytosis (Table 2).

RIFAMPIN

Rifampin is a potent antituberculous drug that also has antibiotic activity against other bacteria, antichlamydial activity, and in vitro activity against some viruses. It is derived from the bacterium *Streptomyces mediterranei*. Rifampin seems to be as potent an antituberculous agent as isoniazid.

Mode of Action and Main Pharmacologic Properties.—Rifampin is a large, fat-soluble molecule that acts by inhibiting synthesis of RNA. More specifically, it inhibits bacterial DNA-dependent RNA polymerase.

Rifampin is well absorbed when taken orally. After administration of a 600-mg dose in patients with an empty stomach, peak serum concentrations of about 7 μg/ml occur at approximately 2 to 4 hours.[10] Although the peak serum levels are slightly less when the drug is taken after a meal than in the fasting state, this difference is not known to be clinically important.

Rifampin penetrates tissues well and reaches therapeutic levels in the lung, bronchial secretions, cerebrospinal fluid in the presence of inflamed meninges, pleural fluid, other cavitary fluids, liver, bile, and urine. The drug crosses the placental barrier.

Approximately 43% of rifampin is excreted in the bile, and 30 to 40% is excreted in the urine. As the dose of the drug is increased, relatively less is excreted in the bile and relatively more is excreted in the urine. Concomitantly administered probenecid considerably diminishes the hepatic uptake of rifampin and thereby increases serum levels. Rifampin is metabolized to the deacetylated form.

Peritoneal dialysis and hemodialysis do not appreciably eliminate rifampin. The absorption of rifampin may be delayed by *p*-aminosalicylic acid; thus, adequate serum levels may not be attained. Therefore, if these two drugs are used in combination, they should be administered 8 to 12 hours apart.

Spectrum of Activity.—Of note, rifampin has the broadest spectrum, in vitro, of any of the primary antituberculous agents. It inhibits almost all strains of *M. tuberculosis, M. kansasii,* and *M. marinum* and a few strains of *M. avium* organisms. It also has activity against other bacteria, including *Neisseria meningitidis, Staphylococcus aureus, Haemophilus influenzae,* and several species of Enterobacteriaceae.

Adverse Effects.—Rifampin can cause numerous side effects (Table 3).[10] Rash may occur in 0.8% of patients, fever in 0.5%, and nausea and vomiting in 1.5%. The drug confers an orange-pink color to saliva, tears, urine, and sweat and may discolor contact lenses. The patient should be informed about this side effect before therapy is initiated.

Table 2.—**Side Effects Associated With Use of Isoniazid**

Side effect	Comment
Hepatotoxicity	Occurrence increases with aging, the presence of liver disease, concomitant rifampin therapy, and daily ingestion of alcohol
Interactions with other drugs	
Alcohol	Increases metabolism of isoniazid
Aluminum-containing antacids	Decreases absorption of isoniazid
Disulfiram (Antabuse)	May precipitate psychotic episodes
Phenytoin (Dilantin)	Increases blood levels and toxicity of phenytoin
Pellagra	...
Rash	
Anemia	
Involvement of nervous system (see below)	
Nervous system	
Peripheral neuritis	Administration of vitamin B_6 can prevent or decrease the severity
Optic neuritis, Seizures, Other	May be prevented or decreased in severity by administration of vitamin B_6
Hypersensitivity	...
Fever	
Rash	
Purpura	
Urticaria	
Other	See text

From Van Scoy RE, Wilkowske CJ: Antituberculous agents: isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide. Mayo Clin Proc 58:233-240, 1983

Rifampin may cause liver disease; the frequency of occurrence of this adverse effect is increased in patients with slow inactivation of the drug (unlike the situation with isoniazid), in patients with prior liver disease, and in those also taking isoniazid. Commonly, liver function tests show minimal abnormalities, which usually disappear while the patient continues to take the drug. Patients must be observed carefully for more substantial degrees of increased enzymes and for jaundice, which occurs in 0.6% of patients who take rifampin; if these side effects occur, use of the drug should be discontinued. In patients taking both isoniazid and rifampin, a predominant increase in serum concentrations of alkaline phosphatase and bilirubin suggests rifampin-induced toxicity;[18] a predominant increase in transaminase levels may be due to toxicity from isoniazid, rifampin, or both drugs.

High-dose intermittent therapy or reinstitution of rifampin therapy after a drug-free interval has resulted in many side effects. Some have been proved to be antibody-mediated immune reactions (such as autoimmune anemia and thrombocytopenia), and others are presumed to be immune reactions (for example, acute renal failure, chills, fever, myalgia, arthralgia, vomiting, diarrhea, and hepatorenal syndrome).[19] Fatal reactions have been reported.

Another group of side effects is related to the ability of rifampin to induce the action of detoxifying or conjugating liver enzymes. This activity may result in decreased effectiveness of certain medications because they are then excreted more rapidly by the liver. Examples of such effects include (1) breakthrough bleeding and pregnancy while the patient is taking birth control pills, (2) adrenal insufficiency during corticosteroid replacement therapy, (3) decreased anticoagulant effect of warfarin drugs, and (4) diminished activity of orally administered hypoglycemic agents, methadone, and digitalis preparations.[16] Drug-drug interactions with imidazoles, such as fluconazole, have been reported.

Rifampin has been incriminated as a cause of immunosuppression. The understanding of all the mechanisms involved and of the extent of immunosuppression is incomplete. Currently, this effect does not seem to be of major clinical importance. Rifampin may also be associated with various gastrointestinal disturbances and nervous system disorders.

STREPTOMYCIN

Streptomycin belongs to the aminoglycoside group of antibiotics discussed earlier in this symposium.[20] Unfortunately, at the time of this writing, streptomycin is not available.

Mode of Action and Main Pharmacologic Properties.—The mode of action and the main pharmacologic properties of the aminoglycoside antibiotics have been discussed previously in this series.[20]

Spectrum of Activity.—Streptomycin is active in vitro against most *M. tuberculosis, M. kansasii,* and *M. marinum* organisms. Most *M. avium* organisms are resistant to streptomycin.

Adverse Effects.—Edson and Terrell[20] have discussed the adverse effects of the aminoglycosides in general in an earlier contribution in this series. Although streptomycin may cause renal toxicity, the toxic effects are considerably less than those associated with other frequently used aminoglycosides. Ototoxicity is the major toxic effect of streptomycin (Table 4). Vestibular toxicity, manifested by vomiting, tinnitus, and vertigo (often preceded by headache), is more common than hearing loss, but hearing loss may also occur and it may be permanent. Ototoxicity is related to the dosage of the drug and the duration of treatment. Avoidance of excessive doses is imperative, particularly in elderly patients and in those with renal insufficiency.[9]

Elderly patients adjust to vestibular toxicity less well than do young persons; therefore, physicians may be hesitant

Table 3.—**Side Effects Associated With Use of Rifampin**

Side effect	Comment
Body fluids become orange-pink	Warn patients
Liver disease	...
Transient abnormalities	
Severe hepatotoxicity	
Associated with intermittent therapy	
Anemia	Immune mechanism
Thrombocytopenia	Immune mechanism
Leukopenia	Presumed immune mechanism
Acute renal failure	
Chills, fever, myalgia, arthralgia, vomiting, diarrhea	
Interactions between rifampin and other drugs	
Birth control pills	Induction of activity of liver enzymes causes decreased levels of all these drugs
Adrenocorticosteroids	
Warfarin	
Orally administered hypoglycemic agents	
Methadone	
Digitalis derivatives	
Hypersensitivity	...
Immunosuppression	Mechanism unclear; probably of little or no importance
Other	
Gastrointestinal symptoms	Usually mild
Central nervous system symptoms	...

From Van Scoy RE, Wilkowske CJ: Antituberculous agents: isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide. Mayo Clin Proc 58:233-240, 1983

about prescribing streptomycin for older patients. Periodic testing with use of audiography and caloric tests of vestibular function may be helpful, especially in bedridden patients. Patients may also be tested by having them rapidly turn 180 degrees while walking, to check for loss of balance. Use of streptomycin should almost always be avoided in pregnant patients.

ETHAMBUTOL

Ethambutol is a synthetic, orally administered antituberculous agent that has essentially replaced *p*-aminosalicylic acid as a second, third, or fourth drug in multidrug regimens. It is bacteriostatic. Although ethambutol has been administered to women during pregnancy without detectable effect on the fetus, the available data are limited, and the risks must be weighed against the benefits of treatment before this drug is recommended for use in pregnant women or women of childbearing age. Ocular toxicity may be difficult to monitor in children younger than 6 years of age; thus, ethambutol is not recommended for use in this age-group.

Mode of Action and Main Pharmacologic Properties.—Ethambutol is the dextro isomer of 2,2′-(ethylenediimino)di-1-butanol dihydrochloride. Chemically, it is unlike other antituberculous agents. The drug is effective against only actively growing cells.

Ethambutol is well absorbed after oral administration, and peak serum concentrations of 2 to 5 μg/ml occur 2 to 4 hours after administration of a single dose of 15 mg/kg. Absorption is unaffected by the ingestion of food. In patients with normal renal function, serum levels become undetectable 24 hours after the last dose has been taken. The intraerythrocytic level is approximately twice the plasma level. About two-thirds of the dose is excreted unchanged in the urine, and about 15% is excreted in the urine in the form of various metabolites.[10] For patients who are unable to swallow pills, the manufacturer suggests crushing the tablets and mixing them with apple juice or applesauce.

Spectrum of Activity.—Although most *M. tuberculosis* and *M. marinum* organisms are sensitive to ethambutol, as are approximately 50% of *M. kansasii* organisms, *M. avium* is consistently resistant to this agent.

In vitro data may serve as an approximate guide for therapy, but the clinical response should be the major factor in monitoring treatment of mycobacteria other than tuberculosis (formerly called atypical mycobacterial infections). The concentrations of 5 to 10 μg/ml used in tabulating the minimal inhibitory concentrations are at or above the peak serum levels often achieved.

Adverse Effects.—Ethambutol is a relatively safe drug when the recommended dosages are used. Ocular toxicity (decreased visual acuity, loss of green color perception, cen-

Table 4.—**Side Effects Associated With Use of Streptomycin**

Side effect	Comment
Ototoxicity	Related to dosage and duration of administration; vestibular more common than auditory toxicity; less well tolerated by elderly persons than by younger persons
Neuromuscular blockade	Dose-related effect; uncommon
Renal toxicity	Milder than that associated with other aminoglycosides
Hypersensitivity	...
Rash, urticaria	
Fever	
Anaphylaxis	
Cytopenia	

From Van Scoy RE, Wilkowske CJ: Antituberculous agents: isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide. Mayo Clin Proc 58:233-240, 1983

Table 5.—**Side Effects Associated With Use of Ethambutol**

Side effect	Comment
Optic neuritis	Dose-related effect; usually reversible
Hyperuricemia	Attributable to decrease in clearance of urate
Rash	...
Anaphylactic shock	...
Miscellaneous	Difficult to determine whether reactions are caused by ethambutol or by a concomitantly administered drug

From Van Scoy RE, Wilkowske CJ: Antituberculous agents: isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide. Mayo Clin Proc 58:233-240, 1983

tral scotomas, or, less commonly, a peripheral visual field defect) is a dose-related phenomenon that occurs in perhaps 5% or fewer of patients who receive 25 mg/kg per day or less[10] (Table 5). This toxic effect is usually reversible when use of the drug is promptly discontinued.[21] In one report, ocular toxicity was noted in only 10 of 2,184 patients; in all but 1 patient, this toxic effect occurred only after the second month of treatment. Only two patients had symptoms, and eight cases were detected on a routine examination of the eyes.[22]

Patients should be tested for visual acuity and green color perception before and periodically during therapy with ethambutol. If a dosage of more than 15 mg/kg per day is used, tests should be conducted monthly. Because toxicity may be unilateral, each eye should be tested independently. Some physicians also advise patients to read the fine print in newspapers. If the patient notices a difference in visual acuity in either eye, medical attention should be sought immediately.

Serum concentrations of uric acid may be increased in patients who receive ethambutol, probably as a result of decreased clearance of renal urate. Such increases occur by the third week of therapy.[23]

As with most drugs, rash and anaphylactic shock may occur with use of ethambutol. Miscellaneous reactions such as peripheral neuritis and symptoms involving the gastrointestinal and central nervous systems have occurred, but these may have been due to concomitantly administered drugs rather than to ethambutol (Table 5). Thrombocytopenia has recently been reported as an additional side effect.[24]

PYRAZINAMIDE

Pyrazinamide, an analogue of nicotinamide, is well absorbed from the gastrointestinal tract and is widely distributed throughout the body. Pyrazinamide is considered bactericidal to actively dividing organisms and eliminates bacilli that are metabolizing slowly or irregularly.

Peak plasma concentrations of 45 μg/ml occur approximately 2 hours after administration of an oral dose of 1 g. The major route of excretion of pyrazinamide is by glomerular filtration, but the drug is also hydrolyzed and then hydroxylated. The usual dosage is 15 to 30 mg/kg per day or 50 to 70 mg/kg twice weekly.

In the older medical literature, pyrazinamide was reported to be hepatotoxic in up to 15% of patients. In recent studies, however, hepatotoxicity developed in only 1 to 5% of patients who received isoniazid, rifampin, and pyrazinamide. Pyrazinamide interferes with the excretion of urate by decreasing its tubular secretion. High serum concentrations of uric acid may result, and clinical manifestations of gout may become evident. Nausea, vomiting, arthralgias, and drug-induced fever may also occur (Table 6).

QUINOLONES (INCLUDING CIPROFLOXACIN)

The quinolone antimicrobial agents are discussed in a separate article in this symposium.[25] Although norfloxacin has only minimal activity against mycobacteria, several other quinolones, including ciprofloxacin and ofloxacin, seem to have appreciable antimycobacterial activity. Quinolones readily penetrate cells, an important criterion for effective treatment of tuberculosis. A report by Leysen and co-workers[26] presents useful information on the new quinolones.

INDICATIONS FOR ANTITUBERCULOUS AGENTS

Discussion of treatment of leprosy and mycobacteria other than tuberculosis is beyond the scope of this article. Physicians should refer patients with infections due to mycobacteria other than tuberculosis, those with drug-resistant tuberculosis, and those who require re-treatment of tuberculosis to a medical facility with extensive experience with these problems. Relatively new antimycobacterial agents that may be helpful not only against *M. tuberculosis* but also against mycobacteria other than tuberculosis include clofazimine, ansamycin, quinolone agents such as ciprofloxacin and ofloxacin, and certain β-lactam agents.

Table 6.—**Side Effects Associated With Use of Pyrazinamide**

Side effect	Comment
Hepatitis	Little or no increase in hepatotoxicity when 15 to 30 mg/kg dose is added to isoniazid and rifampin
Gastrointestinal disturbance	...
Hyperuricemia	Acute gout uncommon
Arthralgias	...
Drug-induced fever	...

Table 7.—**Recommended Dosages for Initial Treatment of Tuberculosis***

Drug	Daily dose (mg/kg)		Maximal daily dose (g)	Twice-weekly dose (mg/kg)	
	Children	Adults		Children	Adults
Isoniazid	10-20, p.o. or i.m.	5, p.o. or i.m.	300 mg	20-40; maximum, 900 mg	15; maximum, 900 mg
Rifampin	10-20, p.o.	10, p.o.	600 mg	10-20; maximum, 600 mg	10; maximum, 600 mg
Pyrazinamide	15-30, p.o.	15-30, p.o.	2-3	50-70	50-70
Streptomycin	20-40, i.m.	15, i.m.	1	25-30, i.m.	25-30, i.m.
Ethambutol†	15-25, p.o.	15-25, p.o.	2.5	50	50
Pyridoxine	10-50 mg/day for those patients who are pregnant or who have diabetes, peripheral neuropathy, uremia, alcoholism, malnutrition, or seizures or other conditions in which neurologic disorders may be likely				

*Doses should be adjusted for renal insufficiency when appropriate. i.m. = intramuscularly; p.o. = perorally.
†Not recommended for children younger than 6 years of age.
Modified from Van Scoy RE, Wilkowske CJ: Antituberculous agents. Mayo Clin Proc 62:1129-1136, 1987.

Several general principles are important in the treatment of tuberculosis. (1) The number of drugs needed increases with the number of bacilli found in the lesions. (2) The number of drugs used can be reduced after a decrease in the number of bacilli is evident. (3) A single drug should never be added to an apparently failing regimen. (4) Noncompliance of the patient in taking prescribed medications is the most common reason for therapeutic failure. (5) The presence of drug resistance should be suspected in patients in whom treatment has failed, patients who have been exposed to others with resistant organisms, patients from Africa, Asia, and Central or South America, patients with cavitary disease or alcoholism, "homeless" patients, unreliable patients including drug abusers, and patients in whom cultures remain positive after 3 months of therapy.

Hospitalization may be necessary for diagnosis and initial supportive care, but thereafter patients can usually be treated at home. Early return to work is routine when the patient is no longer considered contagious. Restriction of activity, unusual rest periods, and "fresh mountain air" are not indicated for the modern-day treatment of tuberculosis.

Treatment Regimens.—Concise reviews of antituberculous drugs, rationale for use, and treatment regimens have been published by the Centers for Disease Control and the American Thoracic Society and others.[2,27] As mentioned earlier, extrapulmonary tuberculosis should be treated with the same regimens as pulmonary tuberculosis.

Six- and 9-month regimens are recommended. The recommended dosages of the various drugs used for the initial treatment of tuberculosis are shown in Table 7. The 6-month regimen is particularly useful for patients who must be under surveillance during therapy. The 6-month regimen is as follows: isoniazid, rifampin, and pyrazinamide daily for 2 months and then isoniazid plus rifampin as either the daily regimen or the twice-weekly regimen for 4 more months. The 9-month regimen consists of isoniazid plus rifampin daily for 2 months, followed by daily or twice-weekly isoniazid and rifampin for 7 more months, for a total of 9 months of therapy.

Both the 6- and the 9-month treatment regimens apply only when (1) the organisms are known to be sensitive to the drugs used; (2) patients are monitored monthly for compliance and adverse reactions; (3) ethambutol or streptomycin is added if resistant organisms are suspected or if life-threatening or extensive disease is present; (4) HIV-infected patients are treated with three or four drugs daily during the first 2 months of therapy; and (5) the duration of treatment for HIV-infected patients is at least 9 months and is continued for at least 6 months beyond substantiated conversion of cultures (negative cultures).

Children.—Ethambutol is generally not used in children whose visual acuity cannot be monitored, such as those younger than 6 years of age. Hilar adenopathy alone or other abnormalities evident on the chest roentgenogram necessitate the use of at least two drugs. Drug susceptibility of the parents of the child is particularly important in choosing regimens for children.

Pregnant Women.—Isoniazid and rifampin can be used during pregnancy, in conjunction with ethambutol if isoniazid resistance is suspected. Use of pyrazinamide should be avoided in pregnant women because the available data on teratogenicity are inadequate.[2] Therefore, the 6-month regimen cannot be used. Breast-feeding is permitted because toxicity from medication is not a problem.

Preventive Therapy.—The indications for preventive therapy for tuberculosis are summarized in Table 8. Before preventive therapy is initiated, the presence of active clinical disease should be excluded. Obviously, if the patient has been adequately treated previously, preventive therapy is not

Table 8.—**Indications for Preventive Therapy for Tuberculosis***

†Persons with known or suspected HIV infection and PPD ≥5 mm

†Close contacts of newly diagnosed cases of infectious tuberculosis and PPD ≥5 mm‡

†Recent tuberculin skin test converters (≥10-mm increase within a 2-yr period if <35 yr old; ≥15-mm increase for those 35 yr or older)

†Previously untreated or inadequately treated persons with chest roentgenograms that show fibrotic lesions compatible with old healed tuberculosis and PPD ≥5 mm

†Persons with PPD ≥10 mm and medical conditions that have been reported to increase the risk of tuberculosis including:

Intravenous drug use	Silicosis
Diabetes mellitus	Fibrotic lesions on chest roentgenogram
Prolonged corticosteroid therapy	Immunosuppressive therapy
End-stage renal disease	Hematologic disease
Intestinal bypass	Postgastrectomy
Carcinoma of oropharynx or upper GI tract	10% or more below ideal body weight

†Persons in the following high-risk groups who are <35 yr of age and PPD ≥10 mm:
Foreign-born persons from high-prevalence countries
Low-income populations, including high-risk minorities
Persons in long-term-care facilities (including prisons)

Other persons <35 yr of age and PPD ≥15 mm

*GI = gastrointestinal; HIV = human immunodeficiency virus; PPD = purified protein derivative (tuberculin) test.
†Recommendations from the Division of Tuberculosis Control, Center for Prevention Services, Centers for Disease Control, and the American Thoracic Society.
‡Close contacts of infectious cases of tuberculosis, especially children, should be given 3 months of preventive therapy and then have another PPD. If the PPD is again negative and contact with the infectious case of tuberculosis has ceased, therapy may be discontinued.

indicated. Patients should be screened for a history of isoniazid-related hepatic injury or discontinuation of isoniazid therapy because of acute liver disease, daily use of alcohol, peripheral neuropathy, or pregnancy.

The recommended regimen is at least 6 months and preferably 12 months of isoniazid therapy in a dosage of 10 mg/kg per day (maximal daily dose, 300 mg). A 12-month regimen is preferred, particularly for those with HIV infection and those with chest roentgenographic abnormalities consistent with previous tuberculosis. When directly observed therapy is indicated to ensure compliance, 15 mg/kg up to a maximum of 900 mg twice weekly may be used if resources are inadequate to observe daily therapy.[2] Rifampin, 600 mg/day for 1 year, should be considered for close contacts of patients with infectious tuberculosis who excrete isoniazid-resistant organisms.[2]

Monitoring of Therapy.—Baseline and follow-up assessments are indicated for patients treated for tuberculosis (Table 9). Patients should be counseled to avoid daily use of alcohol and overall excessive consumption of alcohol and to be aware of symptoms of toxicity. If symptoms occur, a physician should be consulted. In patients older than 35 years of age, serum transaminase should be determined at the onset of therapy and periodically during therapy. If the transaminase level exceeds 3 to 5 times the upper limit of normal, therapy should be discontinued and further therapy planned. No more than a 1-month supply of medication should be dispensed at one time.

Drug-drug interactions, especially with use of rifampin, should be reviewed; agents frequently incriminated are prednisone, birth control pills and other hormones, phenytoin, warfarin, cyclosporine, and orally administered hypoglycemic agents. The patient should be advised to expect a change in color of body fluids and contact lenses during use of rifampin.

More than 90% of patients should become culture negative after 3 months of therapy. If cultures remain positive after 3 months, careful reevaluation for compliance and resistant organisms is indicated.

State and local health departments can be helpful, not only in supplying antituberculous medications to patients—frequently free of charge—but also in the sometimes tedious job of maintaining careful follow-up surveillance of patients and their contacts.

Table 9.—**Monitoring Assessments During Therapy for Tuberculosis**

Baseline tests	
Hepatic enzymes	Uric acid (if pyrazinamide is used)
Bilirubin	Visual acuity (if ethambutol is used)
Creatinine	Audiometry (if streptomycin is used)
Complete blood cell count	
Baseline counseling (see text)	
Monthly interviewing for:	
Toxicity for hepatitis (nausea, vomiting, loss of appetite, dark urine, jaundice, fever, abdominal discomfort), bleeding problems, numbness, paresthesias, visual changes, vertigo, hearing loss or other ear symptoms (if streptomycin is used)	
Other symptoms	
Monthly testing for:	
Efficacy—sputum, induced sputum, or gastric cultures	
Toxicity—laboratory tests based on symptoms elicited, auditory tests every 2 mo if streptomycin is used	

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End of **Symposium on Antimicrobial Agents,** Part VI.
Part VII will appear in the March issue.