American Thoracic Society
MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Treatment of Tuberculosis and Tuberculosis Infection in Adults and Children

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SUMMARY

Treatment of Tuberculosis

1. A 6-mo regimen consisting of isoniazid, rifampin, and pyrazinamide given for 2 mo followed by isoniazid and rifampin for 4 mo is the preferred treatment for patients with fully susceptible organisms who adhere to treatment. Ethambutol (or streptomycin in children too young to be monitored for visual acuity) should be included in the initial regimen until the results of drug susceptibility studies are available, unless there is little possibility of drug resistance (i.e., there is less than 4% primary resistance to isoniazid in the community, and the patient has had no previous treatment with antituberculosis medications, is not from a country with a high prevalence of drug resistance, and has no known exposure to a drug-resistant case). This four-drug, 6-mo regimen is effective even when the infecting organism is resistant to INH. This recommendation applies to both HIV-infected and uninfected persons. However, in the presence of HIV infection it is critically important to assess the clinical and bacteriologic response. If there is evidence of a slow or suboptimal response, therapy should be prolonged as judged on a case by case basis.

2. Alternatively, a 9-mo regimen of isoniazid and rifampin is acceptable for persons who cannot or should not take pyrazinamide. Ethambutol (or streptomycin in children too young to be monitored for visual acuity) should also be included until the results of drug susceptibility studies are available, unless there is little possibility of drug resistance (see Section 1 above). If INH resistance is demonstrated, rifampin and ethambutol should be continued for a minimum of 12 mo.

3. Consideration should be given to treating all patients with directly observed therapy (DOT).

4. Multiple-drug-resistant tuberculosis (i.e., resistance to at least isoniazid and rifampin) presents difficult treatment problems. Treatment must be individualized and based on susceptibility studies. In such cases, consultation with an expert in tuberculosis is recommended.

5. Children should be managed in essentially the same ways as adults using appropriately adjusted doses of the drugs. This document addresses specific important differences between the management of adults and children.

6. Extrapulmonary tuberculosis should be managed according to the principles and with the drug regimens outlined for pulmonary tuberculosis, except for children who have miliary tuberculosis, bone/joint tuberculosis, or tuberculous meningitis who should receive a minimum of 12 mo of therapy.

7. A 4-mo regimen of isoniazid and rifampin is acceptable therapy for adults who have active tuberculosis and who are sputum-smear and culture negative, if there is little possibility of drug resistance (see Section 1 above).

6. The major determinant of the outcome of treatment is patient adherence to the drug regimen. Careful attention should be paid to measures designed to foster adherence and to ensure that patients take the drugs as prescribed. The use of fixed drug combinations may enhance patient adherence and may reduce the risk of inappropriate monotherapy, and it may prevent the development of secondary drug resistance. For this reason, the use of such fixed drug combinations is strongly encouraged in adults. Virtually all the treatment regimens may be given intermittently if directly observed, thus assuring adherence.

Treatment of Tuberculosis Infection

1. Preventive therapy with isoniazid given for 6 to 12 mo is effective in decreasing the risk of future tuberculosis in adults and children with tuberculosis infection demonstrated by a positive tuberculin skin test reaction. The appropriate criterion for defining a positive skin test reaction depends on the population being tested. For adults and children with HIV infection, close contacts of infectious cases, and those with fibrotic lesions on chest radiograph,

This Statement is one of a series of four Statements on diagnosis, treatment, and control of tuberculosis. For information on diagnostic methods, refer to (I) Diagnostic standards and classification of tuberculosis. Am Rev Respir Dis 1990;142: 725-35; and (2) The tuberculin skin test Am Rev Respir Dis 1981;124:356–63. For information on screening for tuberculosis, management of contacts, and organization of control programs, refer to (3) Control of tuberculosis. Am Rev Respir Dis 1992;146:1623–33.

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a reaction of ≥ 5 mm is considered positive. For other at-risk adults and children, including infants and children younger than 4 yr of age, a reaction of ≥ 10 mm is positive. Persons who are not likely to be infected with *Mycobacterium tuberculosis* should generally not be skin tested. If a skin test is performed on a person without a defined risk factor for tuberculosis infection, ≥ 15 mm is positive.

2. Persons with a positive skin test and any of the following risk factors should be considered for preventive therapy regardless of age: persons with HIV infection; persons at risk for HIV infection with unknown HIV status; close contacts of sputum-positive persons with newly diagnosed infectious tuberculosis; newly infected persons (recent skin test convertors); and persons with medical conditions reported to increase the risk of tuberculosis (i.e., diabetes mellitus, adrenocorticosteroid therapy and other immunosuppressive therapy, intravenous drug users, hematologic and reticuloendothelial malignancies, end-stage renal disease, and clinical conditions associated with rapid weight loss or chronic undernutrition). In some circumstances persons with negative skin tests should also be considered for preventive therapy. These include children who are close contacts of infectious cases and anergic HIV-infected adults at increased risk of tuberculosis. Tuberculin-positive adults with abnormal chest films that show fibrotic lesions likely representing old healed tuberculosis and adults with silicosis should usually receive 4-mo multidrug chemotherapy although 12 mo of isoniazid preventive therapy is an acceptable alternative.

Persons who are known to be HIV-infected and who are contacts of patients with infectious tuberculosis should be carefully evaluated for evidence of tuberculosis. If there are no findings suggestive of current tuberculosis, preventive therapy with isoniazid should be given. Because HIV-infected contacts are not managed in the same way as those who are not HIV-infected, HIV testing is recommended if there are known or suspected risk factors for acquisition of HIV infection.

3. In the absence of any of the above risk factors, persons younger than 35 yr of age with a positive skin test in the following high incidence groups should also be considered for preventive therapy: foreign-born persons from high-prevalence countries; medically undersewed low-income persons from high-prevalence populations (especially blacks, Hispanics, and Native Americans); and residents of facilities for long-term care (e.g., correctional institutions, nursing homes, and mental institutions).

4. Twelve months of preventive therapy is recommended for adults and children with HIV infection and other conditions associated with immunosuppression. Persons without HIV infection should receive at least 6 mo of preventive therapy. The American Academy of Pediatrics recommends that children receive 9 mo of therapy.

5. In patients who have a positive tuberculin skin test and either silicosis or a chest radiograph demonstrating old fibrotic lesions, and who have no evidence of active tuberculosis, acceptable regimens include: (7) 4 mo of isoniazid plus rifampin, or (2) 12 mo of isoniazid, providing that infection with drug-resistant organisms is judged to be unlikely.

6. In persons younger than 35 yr of age, routine monitoring for adverse effects of isoniazid should consist of a monthly symptom review. For persons 35 yr of age and older, hepatic enzymes should be measured prior to starting isoniazid and monitored monthly throughout treatment, in addition to monthly symptom reviews. Other factors associated with an increased risk of hepatitis include daily use of alcohol, chronic liver disease, and injection drug use. There is also evidence to suggest that postpubertal black and Hispanic women are at greater risk for hepatitis. Certain medications taken concurrently with isoniazid may increase the risk of hepatitis or drug interactions. More careful monitoring should be considered in these groups, possibly including more frequent laboratory monitoring.

7. Persons who are presumed to be infected with isoniazid-resistant organisms should be treated with rifampin rather than with isoniazid.

8. As with treatment of tuberculosis, the key to success of preventive therapy is patient adherence to the prescribed regimen. Although not evaluated in clinical studies, directly observed, twice-weekly preventive therapy may be used for at-risk adults and children who cannot or will not reliably self-administer therapy.

BACKGROUND

Historically, the American Thoracic Society (ATS) and the Centers for Disease Control (CDC) have provided guidance on the diagnosis, treatment, prevention, and control of tuberculosis in the United States and Canada. The ATS-CDC recommendations have been contained, for the most part, in three official joint Statements: "Diagnostic Standards and Classification of Tuberculosis," "Treatment of Tuberculosis and Tuberculosis Infection in Adults and Children," and "Control of Tuberculosis:' A separate ATS statement, "Diagnosis and Treatment of Disease Caused by Nontuberculous Mycobacteria," containing updated information previously included in the joint statements has recently been issued (1).

Because the technology applicable to the diagnosis, treatment, and control of tuberculosis continues to evolve, periodically it is necessary to revise these Statements. This revision is occasioned by accumulated information on the use of short-course regimens in adults with extrapulmonary tuberculosis and in children, changing guidelines for the administration of preventive therapy, and the emerging problems of tuberculosis in persons with HIV infection, including multidrug-resistant disease. This Statement was developed by the ATS and the CDC in collaboration with the Infectious Disease Society of America and the American Academy of Pediatrics.

The development of specific chemotherapeutic agents revolutionized the prognosis of tuberculosis and tuberculosis infection, making tuberculosis truly curable and preventable. Yet, for a variety of reasons, primarily related to the long duration of drug-taking and to the difficulties of organizing health services to provide diagnostic, treatment, and prevention interventions effectively and efficiently, the promise of chemotherapy has not been fully realized (2).

Drug treatment of tuberculosis should be viewed as both a personal health measure intended to cure the sick patient and as a public health measure intended to interrupt transmission of tubercle bacilli in the community. Treatment of tuberculosis infection with isoniazid prevents disease in the treated person and spares others the possibility of ever becoming infected from contact with that person.

TREATMENT OF TUBERCULOSIS

In the years since the advent of antituberculosis chemotherapy, controlled clinical trials have yielded three basic principles upon which recommendations for treatment are based: (7) regimens for treatment of disease must contain multiple drugs to which the organisms are susceptible, (2) the drugs must be taken regularly, and (3) drug therapy must continue for a sufficient period of time. The aim of treatment should be to provide the safest and most effective therapy in the shortest period of time (3). There are a large number of possible combinations of drugs and rhythms of

administration. But the initial phase of treatment is crucial for preventing emerging drug resistance and determining the ultimate outcome of the regimen. Despite considerable price variation from time to time and place to place, short-course regimens rely heavily on generally expensive drugs; however, these regimens are probably more cost effective than cheaper regimens, and drug cost should not preclude access to effective and appropriate treatment. Utilization of resources and the potential for adverse reactions are also considerations in selecting a treatment regimen.

Any regimen is irrelevant if drugs do not enter the patient's body. Promoting and monitoring adherence to the drug regimen are essential for treatment to be successful. A variety of techniques have been developed to assist in identifying the nonadherent patient. All patients should be asked routinely about their adherence with medication taking, and sporadic urine tests and pill counts may be used to monitor drug ingestion. Record systems for clinic appointments and drug pickups are very important to identify persons who fail to return for follow-up visits. An effective communication system is also needed to ensure that failure to keep appointments comes to the attention of the responsible public health officials. To improve adherence a number of modifications in the organization of treatment have been tried with varying degrees of success. These include setting clinic hours and locations to suit the patients' needs and giving directly observed treatment in the clinic, home, workplace, or other location. The offering of incentives and enablers, such as food, carfare money, babysitting services, or small gifts, may improve adherence by facilitating the patients' medication-taking and appointment-keeping.

Tuberculosis control depends on more than just the science of chemotherapy; chemotherapy can be successful only within the framework of the overall clinical and social management of patients and their contacts. The ultimate elimination of tuberculosis requires an organized and smoothly functioning network of primary and referral services based on cooperation between clinicians and public health officials, between health care facilities and community outreach programs, and between the private and public sectors of medical care.

DRUGS IN CURRENT USE

Isoniazid

Isoniazid is the most widely used of the antituberculosis agents. In many respects it is an ideal agent- bactericidal, relatively nontoxic, easily administered, and inexpensive. It is highly active against *M. tuberculosis* (most strains being inhibited in *vitro* by concentrations of 0.05 to 0.20 μg/ml). Absorption from the gastrointestinal tract is nearly complete, with peak blood concentrations occurring 1 to 2 h after administration. A usual dose of 3 to 5 mg/kg body weight produces a peak concentration of approximately 5 μg/ml. The drug penetrates well into all body fluids and cavities, producing concentrations similar to those found in serum.

Hepatitis is the major toxic effect of isoniazid. In a study of 13,838 patients being given isoniazid alone as preventive therapy, the rate of hepatitis increased directly with increasing age to 65 yr, being 0% for those younger than 20 yr of age; 0.3%, 20 to 34 yr of age; 1.2%, 35 to 49 yr of age; 2.3% 50 to 64 yr of age. Alcohol consumption was also identified as a risk cofactor (4).

Peripheral neuropathy, most likely caused by interference with metabolism of pyridoxine, is associated with isoniazid administration, but it is uncommon at a dose of 5 mg/kg. In persons with conditions in wtiich neuropathy is common (diabetes, uremia, alcoholism, malnutrition), pyridoxine should be given with isoniazid. It is also advisable to give pyridoxine with isoniazid to women who are pregnant and to persons who have a seizure disorder. Mild central nervous system effects are common with isoniazid.

The interaction of isoniazid and phenytoin increases the serum concentration of both drugs. When these drugs are given concomitantly, the serum level of phenytoin should be monitored, and the phenytoin dosage decreased if necessary.

Rifampin

Rifampin is bactericidal for *M. tuberculosis.* The drug is relatively nontoxic and is easily administered. It is quickly absorbed from the gastrointestinal tract, with peak serum concentrations (of 6 to 7 μg/ml) occurring 1.5 to 2 h after ingestion. Most strains of *M. tuberculosis* are inhibited in vitro by concentrations of 0.5 μg/ml. Although approximately 75% of the drug is protein-bound, it penetrates well into tissues and cells. Penetration through noninflamed meninges is poor, but therapeutic concentrations are achieved in cerebrospinal fluid when the meninges are inflamed.

The most common adverse reaction to rifampin is gastrointestinal upset. Other reactions include skin eruptions, hepatitis, and, rarely, thrombocytopenia and cholestatic jaundice. In general, the frequency of these reactions is quite low.

Because rifampin induces hepatic microsomal enzymes, it may accelerate clearance of drugs metabolized by the liver. These include methadone, coumadin derivatives, glucocorticoids, estrogens, oral hypoglycemic agents, digitoxin, antiarrhythmic agents (quinidine, verapamil, mexiletine), theophylline, anticonvulsants, ketoconazole, and cyclosporin (5, 6). By accelerating estrogen metabolism, rifampin may interfere with the effectiveness of oral contraceptives. Current literature should be consulted concerning other possible drug interactions (7).

In adults, intermittent administration of doses of rifampin larger than 10 mg/kg may be associated with thrombocytopenia, an influenzalike syndrome, hemolytic anemia, and acute renal failure. These reactions are uncommon at the recommended dose of 10 mg/kg.

Rifampin is excreted in urine, tears, sweat, and other body fluids, and it colors them orange. Patients should be advised of discoloration of body fluids and of possible permanent discoloration of soft contact lenses.

Pyrazinamide

Pyrazinamide is bactericidal for *M. tuberculosis* in an acid environment. The drug is active against organisms in macrophages, presumably because of the acid environment within the cell. Absorption from the gastrointestinal tract is nearly complete, with peak serum concentrations occurring approximately 2 h after ingestion. Serum concentrations generally range from 30 to 50 μg/ml with doses of 20 to 25 mg/kg. Pyrazinamide penetrates well into most tissues, including the CSF. At a pH of 5.5, the minimal inhibitory concentration of pyrazinamide for *M. tuberculosis* is 20 μg/ml.

The most important adverse reaction to pyrazinamide is liver injury. There does not appear to be a significant increase in hepatotoxicity when pyrazinamide in a dose of 15 to 30 mg/kg is added to a regimen of isoniazid and rifampin during the initial 2 mo of therapy (8). Hyperuricemia occurs frequently, occasionally accompanied by arthralgia, but acute gout is uncommon. Treatment with salicylates generally provides symptomatic relief of pyrazinamide-related arthralgia. Skin rash and gastrointestinal intolerance are also seen.

Ethambutol

Ethambutol in usual doses is generally considered to have a bacteriostatic effect on *M. tuberculosis.* It may have a bacteriocidal

effect when given in the higher dosage used for intermittent therapy. The drug is easily administered and has a low frequency of adverse reactions. Peak plasma concentrations occur 2 to 4 h after ingestion. With doses of 15 mg/kg the peak concentration is approximately 4 μg/ml. In persons with normal renal function, serum half-life is approximately 4 h. The half-life is prolonged, and the drug accumulates in persons with renal insufficiency.

Most strains of *M. tuberculosis* are inhibited *in vitro* by concentrations of the drug in a range from 1 to 5 μg/ml. Cerebrospinal fluid concentrations of ethambutol are low even in the presence of meningeal inflammation, averaging 1 to 2 μg/ml after a dose of 25 mg/kg.

Retrobulbar neuritis is the most frequent and serious adverse effect of ethambutol. Symptoms include blurred vision, central scotomata, and red-green color blindness. This complication is dose-related, occurring in less than 1% of persons given a daily dose of 15 mg/kg and increasing with a daily dose of 25 mg/kg. The frequency of ocular effects is increased in patients with renal failure, presumably because of increased serum concentrations of the drug. Visual symptoms commonly precede a measurable decreased visual acuity. Patients should be informed to report any change in vision. In children who are too young for assessment of visual acuity and red-green color discrimination, ethambutol should be used with particular caution; consideration should be given to the use of possible alternative drugs.

Streptomycin

Streptomycin is bactericidal in an alkaline environment. Because the drug is not absorbed from the gut, it must be given parenterally. Peak serum concentration occurs approximately 1 h after an intramuscular dose. With a dose of 15 mg/kg, the peak concentration is in the range of 40 μg/ml. Most strains of *M. tuberculosis* are inhibited *in vitro* at a concentration of 8 μg/ml. The half-life in blood is approximately 5 h. Excretion is almost entirely renal. The drug should be used in reduced dosage and with extreme caution in patients with renal insufficiency. The drug has good tissue penetration; however, it enters the cerebrospinal fluid only in the presence of meningeal inflammation.

The most common serious adverse effect of streptomycin is ototoxicity. This usually results in vertigo, but hearing loss may also occur. Ototoxicity is more likely if other ototoxic drugs are given concomitantly. Streptomycin has less adverse effect on the kidneys than kanamycin and capreomycin, but nephrotoxicity occasionally occurs. Renal toxicity may be increased in patients with preexisting renal insufficiency or with simultaneous use of other nephrotoxic drugs. The risks of ototoxicity and nephrotoxicity are related both to cumulative dose and to peak serum concentrations.

A total cumulative dose of more than 120 g should not be given unless other therapeutic options are not available. Both ototoxicity and nephrotoxicity are more common in persons older than 60 yr of age. Streptomycin should be avoided or used in reduced dosage, if possible, in this age group.

Para-aminosalicylic Acid

Para-aminosalicylic acid is a bacteriostatic antituberculosis drug. The usual therapeutic dose is approximately 150 mg/kg by mouth, or into a maximal dosage of 10 to 12 g/d. The high doses are necessary because para-aminosalicylic acid is rapidly excreted. The delayed release granules should be given with acidic food or drink, such as orange juice. This dose represents a significant sodium load when the tablet preparation is used. The adverse reactions to the drug include a high frequency of gastrointestinal upset (nausea, vomiting, and diarrhea), hypersensitivity reactions in 5 to 10% of patients, and, rarely, hepatitis.

Ethionamide

Ethionamide is a bacteriostatic derivative of isonicotinic acid. It is available in 250-mg tablets. The usual daily dose is 15 to 20 mg/kg, with a maximum daily dosage of 1 g.

Nausea, vomiting, loss of appetite, and abdominal pain are the most common adverse effects of ethionamide. In many patients it is necessary to increase the dose to the full amount gradually. Administering ethionamide at bedtime with an antiemetic drug taken 30 min before the dose, and, occasionally, a hypnotic, is often useful to maintain treatment. Ethionamide may also cause hepatitis although the frequency is probably no greater than with pyrazinamide. Hepatic enzymes (aspartate aminotransferase, alanine aminotransferase) should be monitored monthly, and the drug should be discontinued if there is a fivefold elevation in enzymes even in the absence of symptoms. Other adverse effects that occur with ethionamide include arthralgias, impotence, gynecomastia, photosensitive dermatitis, hypothyroidism, and a metallic taste in the mouth.

Cycloserine

Like ethionamide, cycloserine is a bacteriostatic antituberculosis agent that is useful in certain limited situations. It is available in 250-mg capsules, and the usual dose is 15 to 20 mg/kg, with a maximal dosage of 1 g/d. The major adverse reactions are emotional and behavioral disturbances including psychosis. Patients who have a history of psychologic problems (for example, depression) or who have a chronic psychiatric condition are more likely to experience the central nervous system effects of cycloserine. Regular assessment of the mental status of these patients is recommended in monitoring for these adverse effects. Convulsions and peripheral neuropathy also occur, especially when the drug is used with isoniazid. For this reason 150 mg/d of pyridoxine should be given with cycloserine. Cycloserine interferes with the elimination of phenytoin, especially when taken with isoniazid; generally, the dosage of phenytoin must be reduced.

Capreomycin

Capreomycin is an injectable antituberculosis agent. It is available in l-g vials, and the daily dosage is 15 to 30 mg/kg by intramuscular injection, or 1 g as the maximal dosage. Capreomycin is toxic to the eighth cranial nerve, causing high frequency hearing loss in 3.2 to 9.4% of patients before vestibular dysfunction occurs. An audiogram performed at baseline and again at least every other month while the patient is receiving therapy is recommended in addition to periodic examinations for vestibular function. Renal toxicity is somewhat more common with capreomycin than with streptomycin, and it may be associated with electrolyte disturbances secondary to tubular damage, as well as an elevated creatinine level. Older patients are generally more susceptible to the toxic effects of capreomycin, and the maximal daily dosage should be limited to 750 mg.

Kanamycin

Kanamycin is also an injectable agent. It is available in 75-mg, 500-mg, and l-g vials. The usual daily dosage is 15 to 30 mg/kg given intramuscularly, with a maximal daily dosage of 1 g. Auditory toxicity is more common with kanamycin than with streptomycin and capreomycin. Monthly audiometry is recommended while patients are being treated with this drug. Vestibular toxicity is rare. Renal toxicity occurs at a frequency similar to that of capreomycin, and regular monitoring of serum creatinine is recommended.

Thiacetazone

Although not available in the United States, thiacetazone is used

in many developing countries because it is so inexpensive. Although thiacetazone is biochemically related to isoniazid, it is bacteriostatic and more toxic than isoniazid. The usual adult dosage is 150 mg/d by mouth. Commonly, it is combined in a single tablet containing 300 to 400 mg of isoniazid and 150 mg of thiacetazone. Gastrointestinal upset occurs in as many as 10% of patients taking the drug, and it includes nausea and vomiting. Less frequent adverse effects include jaundice (< 1%), reversible bone marrow suppression (0.2%), and rashes (3.9%). Cutaneous reactions from thiacetazone may be severe and, if the drug is not stopped, an exfoliative dermatitis or Stevens-Johnson syndrome may occur. These reactions are especially frequent in HIV-infected persons, and the drug is contraindicated in this population. Thiacetazone may also potentiate the vestibular toxicity of streptomycin. Geographic variation in adverse effects has been observed, with patients in East Africa tolerating the drug better than Asians.

POTENTIALLY EFFECTIVE DRUGS THAT HAVE NOT BEEN WIDELY USED IN THE THERAPY OF TUBERCULOSIS

There are a number of new drugs that have been evaluated in children or adults for activity against tuberculosis. These include amikacin, quinolones, rifamycin derivatives, clofazimine, and beta-lactams (9). None of these agents has been tested in multidrug regimens for treating tuberculosis; however, the recent increase in the occurrence of multidrug-resistant tuberculosis may create more situations where the use of these drugs must be considered. None of these drugs has been evaluated in well-designed, randomized trials for tuberculosis treatment or prophylaxis, and they should not be used to replace any of the previously recommended drugs until efficacy is established. Among the new drugs that have been studied as antituberculosis agents, the ones that are discussed subsequently include only those that are licensed or those that are available through an investigational new drug (IND) request, in the United States. Appropriate doses and intervals for the use of these drugs for tuberculosis have not been established. When available, doses are provided. If these drugs are used in infants and children, appropriate adjustments should be made in consultation with tuberculosis experts.

Amikacin

Amikacin is highly bactericidal against *M. tuberculosis in vitro.* It is given as a single daily dose of 15 mglkg by intramuscular injection five times weekly. The solution for intravenous use is prepared by adding the contents of a 0.5-g vial to 100 ml sterile diluent (i.e., normal saline, 5% dextrose in water). The total intravenous single daily dose is also 15 mglkg given over 30 min. Average peak serum concentration (Cmax) is 21 μg/ml 1 h after intramuscular administration of 7.5 mglkg single dose (9). The minimal inhibitory concentration (MIC) for amikacin is approximately 4 to 8 μg/ml for a wide range of strains of *M. tuberculosis* (10).

The major side effect of amikacin is nephrotoxicity. The dose or administration frequency of amikacin should be adjusted if renal insufficiency emerges, blood urea nitrogen and creatinine levels should be monitored weekly or biweekly and, if elevated, warrant a creatinine clearance study. Other side effects include vestibular dysfunction, hearing loss, chemical imbalance (decreases in calcium, potassium, and magnesium levels should be monitored weekly or biweekly), circumoral numbness, and minor dizziness. A baseline audiogram should be done prior to treatment and monthly thereafter if the patient is receiving one injectable drug, twice monthly if receiving two. When there is similar susceptibility to capreomycin and amikacin, capreomycin should be used if the patient is 80 yr of age or older since older patients seem to experience more renal and eight-nerve toxicity with amikacin than with capreomycin (11). Amikacin appears to have the advantage of being less ototoxic than kanamycin, and it is less painful when administered by intramuscular injection.

Whenever possible, amikacin concentrations in serum should be measured to assure adequate but not excessive levels. It is desirable to measure peak serum concentrations monthly during therapy (9). Peak concentrations (30 min after intravenous administration or 80 min after intramuscular injection) of 35 to 45 μg/ml are recommended. Dosage should be adjusted as indicated.

Quinolones

A number of fluoroquinolones have been developed that show *in vitro* activity against *M. tuberculosis.* The target of the quinolones is a DNA gyrase. Ofloxacin and ciprofloxacin are compounds in this family that are licensed for use in the United States. Neither of these drugs is licensed for the treatment of tuberculosis.

The MIC of ofloxacin and ciprofloxacin is about 1 μg/ml for a wide range of strains of *M. tuberculosis (12)* compared with a peak serum concentration of 4.3 μg/ml 1 to 2 h after a 750-mg dose of ciprofloxacin and a 4.6-μg/ml peak serum concentration after multiple 400-mg doses of ofloxacin. One study showed a similar MIC for ofloxacin in the macrophage model, and it found the minimal bactericidal concentration (MBC) to be 2 μg/ml; however, the bactericidal activity of ofloxacin was less than that of rifampin (13). Another study found identical MBC levels of 2 μg/ml for both ciprofloxacin and ofloxacin in 7H12 broth medium (14). In general quinolones are well tolerated. Gastrointestinal symptoms, dizziness, and hypersensitivity are the most commonly reported adverse effects. Changes in laboratory parameters that may be associated with adverse effects include elevations of aspartate aminotransferase, alanine aminotransferase, eosinophilia, leukopenia, and elevations of serum creatinine. The quinolones are primarily cleared by renal excretion, and the dosage should be adjusted for those with creatinine clearance of < 50 ml/min. Few long-term studies of the use of quinolones have been carried out but a review by Ball (15) found that toxicity is more dependent on dose than on the duration of therapy. Because the quinolones have been shown to cause arthropathies in studies with immature animals, these drugs should only be used during pregnancy or in children after carefully weighing the risk to the fetus or child against the potential benefits of therapy with these drugs.

Doses of 750 mg ciprofloxacin and 400 mg ofloxacin twice a day are recommended by the manufacturers for the treatment of severe respiratory tract infections. The data on the use of these agents for the treatment of tuberculosis is limited. A study from Japan reported on patients who had chronic cavitary lung tuberculosis who were excreting bacilli resistant to various antituberculosis agents (18). Of 17 patients who received ofloxacin in combination with other antituberculosis agents as single doses of 300 mg daily for 6 to 8 mo, 14 showed a decrease in culture positivity, and a negative conversion occurred in five. No side effects were observed. Another study of ofloxacin reported on 22 patients receiving 300 or 800 mg of ofloxacin in a single daily dose for 9 mo to 1 yr (17). All tolerated the drug well, and there were indications of higher efficacy at the higher dose.

Concomitant administration of quinolones with theophylline may prolong the half-life of theophylline, increase serum levels, and increase the risk of adverse effects caused by theophylline. Antacids with aluminum, magnesium, or calcium and ferrous sulfate may interfere with the absorption of quinolones, if taken together.

Rifabutin

Rifabutin is a rifamycin spiropiperidyl derivative that shows activity in *vitro* against certain rifampin-resistant strains of *M.* tuberculosis. The MIC for strains of *M. tuberculosis* that are susceptible to rifampin are low: < 0.06 μg/L (18). The MIC for rifampin-resistant strains are significantly higher than for the rifampin-susceptible strains (range, 0.25 to 16.0 μg/ml), indicating cross-resistance between these two drugs (18). The wide range of MICs for these strains is an indication that the rifampin-resistant strains have varying degrees of susceptibility to rifabutin.

Rifabutin is rapidly absorbed from the gastrointestinal tract, with peak serum levels of 0.49 μg/ml occurring 4 h after administration of 300 mg (19). The half-life in serum is 16 h, and tissue levels are 5- to lo-fold higher than that in serum. Protein binding for rifabutin appears to be 25% of that seen for rifampin. The drug is eliminated at similar concentrations by the kidney and liver.

The achievable serum and tissue levels of rifabutin are well in excess of the MICs for rifampin-susceptible strains; however, in one study of 21 rifampin-resistant strains, serum concentrations exceeded MICs for only eight of the 21 strains when determined by the 7H11 agar plate method, and five of the 21 strains when determined by the 7H12 broth method (18). The implications for the use of rifabutin in clinical chemotherapy are not yet clear. Strains of *M. tuberculosis* with MICs < 0.5 μg/ml can probably be considered as "moderately susceptible" to rifabutin (18).

In studies of acute and chronic toxicity in several species of animals, rifabutin was of comparable toxicity to, or less toxic than, rifampin. One analysis of rifabutin toxicity in humans found that the most common adverse reactions to rifabutin were hematologic and hepatotoxic reactions. The data suggest that rifabutin is probably not more hepatotoxic than rifampin (19). Other reactions include gastrointestinal upset and hypersensitivity.

Clofazimine

Clofazimine is a substituted iminophenazine bright-red dye that exerts a slow bactericidal effect on *M. leprae.* Clofazimine inhibits mycobacterial growth and binds preferentially to mycobacterial DNA causing inhibition of transcription. In addition to this direct antimycobacterial property, clofazimine in combination with gamma interferon restores the inhibition of phagocytic and microbicidal activities caused by a 2Bkilodalton fraction from *M. tuberculosis,* indicating the possible use of these two phagocyte-priming agents for the immunotherapy of tuberculosis (20).

The mean peak serum concentration of clofazimine after a single oral dose of 300 mg is 1.0 μg/ml. The MICs for *M. avium* isolated from patients without AIDS range from 0.1 to 1.0 μg/ml, and the MICs for isolates from patients with AIDS range from 1.0 to 5.0 μg/ml. The MICs of clofazimine against *M. tuberculosis* have not been published.

Adverse reactions include discoloration of the skin, gastrointestinal upset, severe and life-threatening abdominal pain and organ damage caused by clofazimine crystal deposition, and asymptomatic discoloration of the eye (21).

Combination of beta-Lactam Antibiotics and beta-Lactamase Inhibitors

Amoxicillin is a semisynthetic beta-lactam antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. The addition of a beta-lactamase inhibitor to amoxicillin greatly improves its *in vitro* activity against *M. tuberculosis (22).* The beta-lactam inhibitors (i.e., clavulanic acid) possess no intrinsic antimycobacterial activity, but they are able to inhibit the enzyme in part responsible for the resistance of *M. tuberculosis* to beta-lactam antibiotics. In one *in vitro* study, the MIC of amoxicillin plus clavulanic acid was 4 mg/ml compared with > 32 mg/ml for amoxicillin alone when tested against 27 strains of *M. tuberculosis (22).* After an oral dose of 500 mg of amoxicillin, peak serum concentrations of 7.5 μg/ml are achieved in 2 h. There are no *in vivo* studies using this drug combination against *M. tuberculosis.* Beta-lactam antibiotics penetrate poorly into mammalian cells, and this characteristic may limit the effectiveness of these agents in therapy for tuberculosis (23).

The New Macrolides

The new macrolides are semisynthetic derivatives that differ from erythromycin in the size or substitution pattern of the lactone ring system. Currently available *in vitro* susceptibility tests suggest that the currently available macrolides are unlikely to be effective in the treatment of tuberculosis.

Initial Treatment Regimens (see also Table 1)

A large number of studies performed during the past 45 yr have provided specific information concerning the use of combinations of antituberculosis agents. Several important generalizations can be made from these studies.

1. Isoniazid possesses the best combination of effectiveness, low frequency side effects, and cost of any of the antituberculosis agents and thus should be used for the duration of whatever regimen is used unless there are contraindications or the organisms are resistant to the drug.

2. Despite some scattered reports of good results with 4-mo regimens, in general, relapse rates with regimens of such short duration are unacceptably high. An exception is the adult who, after careful evaluation, is found to have sputum-culture-negative pulmonary tuberculosis. In such adults, 4-mo regimens have a high rate of success.

3. For regimens 6 mo in duration, rifampin and isoniazid are essential for the total duration of therapy.

4. Pyrazinamide, given in the initial phase, improves the efficacy of regimens of less than 9 mo duration.

5. In the doses usually given, substituting ethambutol or streptomycin for pyrazinamide in the initial phase decreases the effectiveness of a regimen.

6. There is good evidence that intermittent administration of appropriately adjusted doses of the drugs after an initial daily phase of treatment as short as 2 wk produces results equal to those of daily administration. Regimens of four drugs given three times weekly throughout the course of treatment give equally good results in adults. Although there are no data available for three times weekly regimens in children, experience with other intermittent regimens suggests that they would be equally efficacious in children.

The above treatment guidelines apply only when the disease is caused by organisms that are susceptible to the standard antituberculosis agents. Rates of initial resistance to antituberculosis drugs have remained low (< 4% to isoniazid) in some parts of the United States.

Outbreaks of disease caused by multiple drug-resistant organisms have been reported with increasing frequency (24-26). In these outbreaks the organisms isolated have been resistant at least to isoniazid and rifampin and frequently to ethambutol and other agents as well. Not unexpectedly, tuberculosis caused by organisms resistant to isoniazid and rifampin has been notable for its poor response to treatment with standard initial regimens. In addition, because the outbreaks of multiple drug-resistant tuber-

TABLE 1

REGIMEN OPTIONS FOR THE PREFERRED INITIAL TREATMENT OF CHILDREN AND ADULTS'

Option 1	Option 2	Option 3
Administer daily isoniazid, rifampin, and pyrazinamide for 8 wk followed by 16 wk of isoniazid and rifampin daily or 2-3 times/wk.† In areas where the isoniazid resistance rate is not documented to less than 4%, ethambutol or streptomycin should be added to the initial regimen until susceptibility to isoniazid and rifampin is demonstrated. Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 mo.	Administer daily isoniazid, rifampin, pyrazinamide, and streptomycin or ethambutol for 2 wk followed by 2 times/wk† administration of the same drugs for 6 wk (by DOT), and subsequently, with 2 times/wk administration of isoniazid and rifampin for 16 wk (by DOT). Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 mo.	Treat by DOT, 3 times/wk† with isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin for 6 mo.* Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 mo.

* Adapted from MMWR Vol. 42/no. RR-7.

† All regimens administered 2 times/wk or 3 times/wk should be monitored by directly observed therapy (DOT) for the duration of therapy.

‡ The strongest evidence from clinical trials is the effectiveness of all four drugs administered for the full 6 mo. There is weaker evidence that streptomycin can be discontinued after 4 mo if the isolate is suspectible to all drugs. The evidence for stopping pyrazinamide before the end of 6 mo is equivocal for the 3 times/wk regimen, and there is no evidence on the effectiveness of this regimen with ethambutol for less than the full 6 mo.

culosis have occurred mainly, although not exclusively, among HIV-infected adults, there has been transmission of infection and rapid progression to disease among their contacts.

Because of the major impact of resistance to isoniazid and rifampin on the response to therapy and because of the public health issues involved, it is essential that physicians initiating therapy for tuberculosis be aware of the prevalence of drug resistance in their communities and of the epidemiologic features of persons most likely to be harboring these organisms. In addition, drug susceptibility testing should be performed on the organisms initially isolated from all patients with newly diagnosed tuberculosis. It is desirable to have access to a laboratory in which both identification of an organism and determination of its susceptibility pattern are done rapidly. At present radiometric or colorimetric detection techniques provide the earliest identification of growth. Even if there is no capability for performing full drug-susceptibility studies, testing for resistance to rifampin could identify strains likely to have multiple drug resistance.

The current minimal acceptable duration of treatment for all children and adults with culture-positive tuberculosis is 6 mo (27). The initial phase of a 6-mo regimen should consist of a 2-mo period of isoniazid, rifampin, and pyrazinamide. Ethambutol (or streptomycin in children too young to be monitored for visual acuity) should be included in the initial regimen until the results of drug susceptibility studies are available, unless there is little possibility of drug resistance (i.e., there is less than 4% primary resistance to isoniazid in the community, and the patient has had no previous treatment with antituberculosis medications, is not from a country with a high prevalence of drug resistance, and has no known exposure to a drug-resistant case). This recommendation is intended to prevent the development of multiple drug-resistant tuberculosis in areas where primary INH resistance is increased. The second phase of treatment should consist of isoniazid and rifampin given for 4 mo. In treating patients with HIV infection it is critically important to assess clinical and bacteriologic response. Treatment should be prolonged if the response is slow or otherwise suboptimal. There is probably a reduced margin of safety in treating patients with HIV infection; therefore, the effect of patient adherence on the outcome is much more crucial. For this reason, directly observed therapy is strongly recommended in this group.

Tuberculosis caused by multiple drug-resistant organisms should be suspected in patients who are not responding to initial therapy or when epidemiologic factors suggest the presence of multiple drug resistance. The principles of management in this setting are described below.

Because HIV-infected patients seem to have a greater frequency of adverse reactions to antituberculosis drugs compared with patients not infected with HIV, patient monitoring must take this into account.

Consideration should be given to treating all patients with directly observed therapy (DOT), which can be given on an intermittent schedule. DOT means observation of the patient by a health care provider or other responsible person as the patient ingests antituberculosis medications. DOT can be achieved with daily, twice-weekly, or thrice-weekly administration of medication. It may be administered to patients in the office or clinical setting, but it is frequently given by a health department worker in the "field," i.e., the patient's home, place of employment, school, or other mutually agreed-upon place. In some cases, staff of correctional facilities or drug treatment programs, home health-care workers, maternal and child health staff, or responsible community or family members may administer DOT.

Several options exist for administering directly observed therapy. Intermittent (i.e., twice-weekly) therapy may be given during the second phase after daily therapy during the initial phase. For those for whom prolonged supervision of daily therapy during the initial phase is impractical, a regimen of daily isoniazid, rifampin, pyrazinamide, and streptomycin or ethambutol for 2 wk, followed by twice-weekly administration of the same drugs for 6 wk and subsequently twice-weekly isoniazid and rifampin for 16 wk has been shown to be highly effective in adults (26). Alternatively, three-times-weekly administration of isoniazid, rifampin, pyrazinamide, and either streptomycin or ethambutol for 6 mo yields equivalent results in adults (29).

These specific intermittent regimens have not been studied in children, but extrapolation from other intermittent regimens suggests that they would be effective.

Nine-month regimens using isoniazid and rifampin are also effective when organisms are fully drug-susceptible (30). Ethambutol or streptomycin (or streptomycin in children too young to be monitored for visual acuity) should be included in the initial regimen until the results of drug-susceptibility studies are available, unless there is little possibility of drug resistance (i.e., there is less than 4% primary resistance to isoniazid in the community, and the patient has had no previous treatment with antituberculosis medications, is not from a country with a high prevalence of drug resistance, and has no known exposure to a drug-resistant case).

Isoniazid and rifampin may be given twice weekly after an initial 1 or 2 mo of daily treatment (31).

Shorter treatment is possible in adults with sputum smear- and culture-negative active pulmonary tuberculosis. Four months of isoniazid and rifampin, preferably with pyrazinamide for the first 2 mo, yields results equivalent to those for patients with culture-positive disease treated with longer regimens (32, 33). This 4-mo regimen is also recommended for adult tuberculin reactors who have a chest film suggesting old healed tuberculosis and for adult reactors who have silicosis and are sputum smear- and culture-negative although 12 mo of isoniazid therapy is an acceptable alternative.

The frequency of adverse reactions to drugs in regimens of 6 to 9 mo in duration varies, depending in part on whether streptomycin is included in the regimen. With streptomycin-containing regimens, approximately 6% of patients have adverse reactions that require modification of the regimen. Without streptomycin, the frequency is approximately 3%. Because ethambutol can be used instead of streptomycin, and it appears to be equally effective, streptomycin toxicity should not be a major factor limiting the success of chemotherapy.

The use of fixed drug combinations may enhance patient adherence and may reduce the risk of inappropriate monotherapy and may prevent the development of secondary drug resistance. For this reason the use of such fixed-dose drug combinations is strongly encouraged in adults.

Monitoring for Adverse Reactions

Adults treated for tuberculosis with the regimens outlined above should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count, and a platelet count (or estimate). Serum uric acid should be measured if pyrazinamide is used, and a baseline examination of both visual acuity and red-green color perception should be obtained for patients to be treated with ethambutol. The purpose of these baseline tests is to detect any abnormality that would complicate the regimen or necessitate its modification. In addition, these baseline tests enable comparison with later measurements should a suspected adverse reaction occur. Baseline tests, except visual acuity, are unnecessary in children unless a complicating condition is known or clinically suspected.

All patients, adults and children, should be monitored clinically for adverse reactions during the period of chemotherapy. They should be instructed to look for symptoms associated with the most common adverse reactions to the medications they are receiving. Patients should be seen by medical personnel at least monthly during therapy and should be specifically questioned concerning such symptoms. All patients with abnormalities detected on baseline should have follow-up of these findings. Routine laboratory monitoring for toxicity in people with normal baseline is generally not necessary. However, if symptoms suggesting drug toxicity occur, then appropriate laboratory testing should be performed to confirm or exclude such toxicity.

EVALUATION OF RESPONSE TO TREATMENT

Patients with Positive Pretreatment Sputum

The response to antituberculosis chemotherapy in patients with positive bacteriology (M. tuberculosis identified in sputum) is best evaluated by repeated examinations of sputum. Sputum examinations at least at monthly intervals are desirable until sputum conversion is documented (weekly sputum smears with quantitation are encouraged). After 2 mo of treatment with regimens containing both isoniazid and rifampin, more than 85% of patients who had positive sputum cultures before treatment should have converted to negative.

Patients whose sputum cultures have not become negative after 2 mo of treatment should be carefully reevaluated. Drug susceptibility tests should be repeated, and treatment should be administered or continued under direct observation. Unless drug resistance is demonstrated, the treatment regimen should be continued with special attention to adherence. If organisms are found to be resistant, the treatment regimen should be modified to include at least two drugs to which the organisms are susceptible and administered under direct observation. Bacteriologic evaluations are valuable for detecting nonresponse to treatment and multidrug resistance, and they should be performed at least at monthly intervals thereafter until cultures become negative.

Patients whose sputum no longer contains *M. tuberculosis* after 2 mo of treatment should have at least one further sputum smear and culture performed at completion of therapy. Radiographic evaluations during treatment are of less importance than sputum examination. However, a chest film at completion of treatment provides a baseline for comparison with any future films.

Patients with susceptible organisms who have completed a standard period of treatment with an isoniazid-rifampin-containing regimen and who have had a prompt and satisfactory bacteriologic response do not need routine follow-up. In some circumstances, however, as when patients have been slow to respond, have significant residual radiographic findings on completion of treatment, or are immunosuppressed, reevaluation 6 mo after completion of treatment may be of value. Patients should be instructed to report promptly the development of any symptoms, particularly prolonged cough, fever, or weight loss. These statements apply to patients whose organisms were fully susceptible to the drugs being used. In patients with organisms resistant to isoniazid and/or rifampin, follow-up evaluations must be individualized.

Patients with Negative Pretreatment Sputum

In all adults with radiographic abnormalities consistent with tuberculosis, vigorous efforts should be made to establish a microbiologic diagnosis. These efforts should include induction of sputum by inhalation of hypertonic saline. Bronchoscopy with appropriate biopsies and bronchoalveolar lavage should be considered for patients unable to produce a satisfactory sputum specimen. If no other diagnosis can be established, presumptive treatment for tuberculosis may be indicated. In such adults, the major indicators of response to therapy are the chest radiograph and clinical evaluation. The intervals at which chest films should be repeated will depend on the clinical circumstances and the differential diagnosis being considered. Failure of the radiograph to improve after 3 mo of chemotherapy is strongly suggestive that the abnormality is the result of either previous (not current) tuberculosis or another process. If the tuberculin reaction is positive and other diagnoses have been excluded, isoniazid and rifampin can be continued for a total of 4 mo. In children with suspect tuberculosis, microbiologic data can be gained from early morning gastric aspirates or urine. In complicated cases or severely ill children, bronchoalveolar lavage should be considered. An aggressive diagnostic approach in children with HIV infection or pneumonia that is unresponsive to standard treatment should be taken. Specimens for smear, culture, and susceptibility tests should be collected from all children for whom culture and susceptibility information is not available in their adult contact whenever possible.

In patients with extrapulmonary tuberculosis, the nature of repeat evaluations should be determined by the site of involvement. In some instances, for example genitourinary tuberculosis, bac-

teriologic examinations may be quite feasible, whereas in disease involving lymph nodes or bones and joints, clinical evaluation is the most practical way of determining response. Evaluations should also be directed toward detecting and quantifying the effects of tuberculosis on the structure and function of the involved systems. For example, evidence of hemodynamic effects should be sought in patients with tuberculous pericarditis, and patients with genitourinary tuberculosis should be evaluated for the presence of ureteral strictures.

MANAGEMENT OF PATIENTS WHOSE TREATMENT HAS FAILED OR WHO HAVE RELAPSED

Patients whose sputum has not converted after 5 to 6 mo of treatment are treatment failures. Susceptibility tests should be obtained on a current sputum specimen. While results are pending, the original drug regimen may be continued or may be augmented by at least three drugs not given previously. The regimen should be adjusted in accordance with the results of the susceptibility tests. Therapy should be administered under direct observation.

In contrast to patients who are treatment failures, in patients who relapse after completing a regimen containing isoniazid and rifampin and whose organisms were susceptible to the drugs at the outset of treatment, the organisms usually remain susceptible (34). Thus, management of these patients generally consists of reinstitution of the regimen previously used. However, drug susceptibility testing should be performed and the regimen modified if resistance is detected. Directly observed therapy should be used.

Patients who relapse after receiving regimens that did not contain both isoniazid and rifampin should be assumed, until proved otherwise, to have organisms that are resistant to the agents that were used previously and managed accordingly.

MANAGEMENT OF PATIENTS WHO HAVE DRUG-RESISTANT DISEASE

Microbial resistance to antimycobacterial drugs may be either initial or secondary. Initial resistance occurs in patients who are not known to have had previous antimycobacterial treatment. Risk factors for initial resistance include exposure to a patient who has drug-resistant tuberculosis, being from a country with a high prevalence of drug resistance, and greater than 4% primary resistance to isoniazid in the community. Secondary resistance occurs in patients who have been treated in the past. The frequency of both types of resistance is to a' large extent determined by the adequacy of tuberculosis treatment programs. Poor treatment programs enable resistant organisms to emerge, producing secondary resistance in inadequately treated patients. These organisms are then transmitted and, when disease occurs, the infected person has "primary" resistant disease.

In the past, primary isoniazid resistance rates in most areas of the United States were < 4%; thus, two- and three-drug regimens for tuberculosis were considered adequate. Community rates of primary isoniazid resistance < 4% may be an indication that an initial regimen of fewer than four drugs is acceptable. However, continued surveillance of drug susceptibility patterns is necessary to ensure that low rates of primary drug resistance continue.

Recently, pockets of tuberculosis caused by organisms that are resistant to at least isoniazid and rifampin have been described. Resistance to both of these potent agents considerably complicates patient management, making a successful outcome much less likely than if susceptibility to one or the other of these two agents were maintained.

The basic principle of managing patients whose organisms are resistant to one or more drugs is administration of at least two agents to which there is demonstrated susceptibility. For patients with isolated isoniazid resistance the recommended 6-mo 4-drug regimen is effective (35). When isolated isoniazid resistance is documented, isoniazid should be discontinued and pyrazinamide should be continued for the entire 6-mo duration of therapy. When isoniazid resistance is documented in the 9-mo regimen without pyrazinamide, isoniazid should be discontinued. If ethambutol was included in the initial regimen, treatment with rifampin and ethambutol should be continued for a minimum of 12 mo (36). If ethambutol was not included initially, susceptibility tests should be repeated, isoniazid should be discontinued, and two new drugs (e.g., ethambutol and pyrazinamide) should be added. The regimen can be adjusted when the results of the susceptibility tests become available.

Unfortunately, good data are not available on the relative effectiveness of various regimens and the necessary duration of treatment for patients with organisms resistant to both isoniazid and rifampin. Moreover, many such patients will have resistance to other first-line drugs (e.g., ethambutol and streptomycin) when drug resistance is discovered. Because of the poor outcome in such cases, it is preferable to give at least three new drugs to which the organism is susceptible. This regimen should be continued at least until bacteriologic sputum conversion is documented, followed by at least 12 mo of two-drug therapy. Often, a total of 24 mo of therapy is given empirically. The role of new agents such as the quinolone derivatives and amikacin in the treatment of multidrug-resistant disease is not known, although these drugs are commonly being used in such cases. Finally, surgery appears to offer considerable benefit and significantly improved cure rate for those patients in whom the bulk of disease can be resected (37).

TUBERCULOSIS IN CHILDREN AND ADOLESCENTS

The basic principles of treatment of tuberculosis in children and adolescents are essentially the same as for adults (36). Nine-month regimens containing isoniazid and rifampin have been demonstrated to have a high rate of success in children and adolescents (39), and hilar adenopathy has been successfully treated with only 6 mo of this combination (40). More recent studies of 6-mo regimens containing pyrazinamide have also produced excellent results with minimal toxicity (41). There are no data related to the ultrashort 4-mo regimen in children and adolescents yet.

Therefore, the short-course regimens recommended for adults are also the regimens of choice for children with pulmonary tuberculosis. The usual doses for daily and twice-weekly treatment in children are shown in tables 2 and 3. Follow-up evaluations after successful completion of therapy should be the same as described for adults.

Beyond the basic approach to treatment of tuberculosis in children, there are several important management considerations.

1. Tuberculosis in infants and children younger than 4 yr of age is much more likely to disseminate; therefore, prompt and vigorous treatment should be started when the diagnosis is suspected.

2. Primary intrathoracic tuberculosis (parenchymal infiltration, hilar adenopathy, or both, in a child with a significant tuberculin skin test reaction) should be treated in the same manner as pulmonary tuberculosis. However, when drug resistance is unlikely, treatment with rifampin and isoniazid for 6 mo supplemented by pyrazinamide in the initial 2 mo is sufficient.

3. Because sputum specimens are less likely to be helpful in children, it may be necessary to rely on the results of cultures and susceptibility tests of specimens from the adult source case

TABLE 2

DOSAGE RECOMMENDATION FOR THE INITIAL TREATMENT OF TUBERCULOSIS IN CHILDREN* AND ADULTS

	Dosage					
	Daily Dose		Twice-Weekly Dose		Thrice-Weekly Dose	
Druas	Children	Adults	Children	Adults	Children	Adults
Isoniazid, mglkg	1 O-20 Max 300 mg	5 Max 300 mg	20-40 Max 900 mg	15 max Max 900 mg	20-40 Max 900 mg	15 max Max 900 mg
Rifampin, mglkg	1 O-20 Max 600 mg	IO Max 600 mg	1 O-20 Max 600 mg	10 Max 600 mg	1 O-20 Max 600 mg	10 Max 600 mg
Pyrazinamide, mglkg	15-30 Max 2 g	15-30 Max 2 g	50-70 Max 4 g	50-70 Max 4 g	50-70 Max 3 g	50-70 Max 3 g
Ethambutol, mg/kg†	15-25	15-25	50	50	25-30	25-30
Streptomycin, mglkg	20-40 Max 1 .O g	15 Max 1.0 g	25-30 Max 1.5 a	25-30 Max 1.5 a	25-30 Max 1.5 g	25-30 Max 1.5 g

* Children ≤ 12 yr of age.

† Ethambutol is generally not recommended for children whose visual acuity cannot be monitored (< 8 yr of age). However, ethambutol should be considered for all children with organisms resistant to other drugs when susceptibility to ethambutol has been demonstrated or suspecitibility is likely.

to "confirm" the diagnosis in the child and to guide the choice of drugs. In cases of suspect drug-resistant tuberculosis or where adult isolates are not available, the aggressive pursuit of early morning gastric aspirates, bronchoalveolar lavage, or tissue diagnosis may have to be entertained.

4. For the same reason, bacteriologic examinations are less useful in evaluating the response to treatment; thus, clinical and radiographic examinations are of relatively greater importance in children. However, hilar adenopathy frequently requires 2 to 3 yr of complete radiographic resolution; a normal chest radiograph is not a necessary criterion for discontinuing antituberculosis drugs.

5. Because it is difficult to monitor for ocular toxicity from ethambutol, this agent is less useful in young children. Streptomycin or pyrazinamide are alternatives.

6. In general, extrapulmonary tuberculosis, including cervical adenopathy, can be treated with the same regimens as pulmonary tuberculosis. Exceptions may be bone and joint disease, disseminated (miliary) disease, and meningitis for which there are inadequate data at present to support 6-mo therapy. In these situations, a minimum of 12 mo of therapy is recommended.

7. Directly observed therapy is preferable unless there is evidence that the patient or parent will comply with therapy.

8. *Management of the newborn infant whose mother (or other household contact) has tuberculosis.* Management of a newborn infant whose mother (or other household contact) is suspected of having tuberculosis is based on individual considerations. If possible, separation of the mother (or contact) and infant should be minimized. Differing circumstances and resulting recommendations are as follows: (7) *Mother (or other household contact) who has a positive tuberculin skin test reaction and no evidence of current disease.* Investigation of other members of the household or extended family to whom the infant may later be exposed is indicated. If no evidence of current disease is found in the mother or extended family, the infant should be tested with a Mantoux test (5 TU PPD) at 4 to 6 wk of age and at 3 to 4 mo of age. When

TABLE 3

SECOND-LINE ANTITUBERCULOUSIS DRUGS"

Drua	Dosaae Forms	Daily Dose in Children and Adults-f	Maximal Daily Dose in Children and Adults	Major Adverse Reactions	Recommended Regular Monitorina
Capreomycin	Vials: 1 g	15 to 30 mglkg, IM	1 g	Auditory, vestibular, and renal toxicity	Vestibular function audiometry, blood urea nitrogen, and creatinine
Kanamycin	Vials: 75 mg 500 mg 1 g	15 to 30 mglkg, IM	1 g	Auditory and renal toxicity, rare vestibular toxicity	Vestibular function, audiometry, blood urea nitrogen, and creatinine
Ethionamide	Tablets: 250 mg	15 to 20 mglkg, PO	1 g	Gastrointestinal disturbance, hepatotoxicity, hypersensitivity	Hepatic enzymes
Para-aminosalicylic acid	Tablets: 500 mg, 1 g Bulk powder Delayed release granules	150 mglkg, PO	12 g	Gastrointestinal disturbance, hypersensitivity hepatoxicity, sodium load	
Cycloserine	Capsules: 250 mg	15 to 20 mglkg, PO	1 g	Psychosis, convulsions, rash	Assessment of mental status

* These drugs are more difficult to use than the drugs listed in table 1. They should be used only when necessary, and they should be given and monitored by health providers experienced in their use.

† Doses based on weight should be adjusted as weight changes.

the family cannot be promptly tested, consideration should be given to the administration of isoniazid (10 mg/kg/d) to the infant until skin testing of the family has excluded contact with a case of active tuberculosis. The infant does not need to be hospitalized during this time if adequate follow-up can be arranged. The mother should also be considered for isoniazid preventive therapy. (2) *Mother who has current disease and is judged to be noncontagious at delivery.* Careful investigation of household members and extended family is mandatory. A chest roentgenogram and Mantoux tuberculin test at 4 to 6 wk of age should be performed on the infant; if these are negative, the infant should be tested again at 3 to 4 mo and at 6 mo. Separation of the mother and infant is not necessary if adherence with treatment by the mother is ensured. The mother can breast feed. The infant should receive isoniazid even if the tuberculin skin test and chest roentgenogram do not suggest tuberculous disease since cell-mediated immunity of a degree sufficient to mount a significant reaction to tuberculin skin testing can only develop as late as 6 mo of age in an infant infected at birth. Isoniazid can be discontinued if the Mantoux skin test is negative at 6 mo of age and no active disease exists in family members. The infant should be examined carefully at monthly intervals. If nonadherence is documented, the mother has AFB-positive sputum (or smear), and supervision is impossible, bacillus Calmette-Guérin vaccine may be considered for the infant. However, the response to the vaccine in infants may be inadequate for prevention of tuberculosis. (3) *Mother who has current disease and is suspected of being contagious at the time of delivery.* The mother and the infant should be separated until the mother is judged to be noncontagious. Otherwise, management is the same as when the disease is judged to be noncontagious to the infant at delivery (see preceding paragraph). (4) *Mother who has hematogenous spread of tuberculosis (e.g., meningitis, miliary disease, or bone involvement).* If the mother has hematogenous spread of tuberculosis, congenital tuberculosis in the infant is possible. If the infant is suspected of having congenital tuberculosis, a PPD Mantoux skin test and chest roentgenogram should be performed promptly, and treatment of the infant should begin at once. If clinical or roentgenographic findings do not support the diagnosis of congenital tuberculosis, the infant should be separated from the mother until she is judged to be noninfectious. The infant should be given isoniazid until 6 mo of age at which time the skin test should be repeated. If the skin test is positive, isoniazid should be continued for a total of 9 mo (38).

SPECIAL CONSIDERATIONS IN TREATMENT

Extrapulmonary Tuberculosis

The basic principles that underlie the treatment of pulmonary tuberculosis also apply to extrapulmonary forms of the disease. Although there have not been the same kinds of carefully conducted controlled trials of treatment for extrapulmonary tuberculosis as for pulmonary disease, increasing clinical experience is indicating that 6- to 9-mo short-course regimens are effective (42). Because of insufficient data, miliary tuberculosis, bone/joint tuberculosis, and tuberculous meningitis in infants and children should receive 12 mo of therapy.

Bacteriologic evaluation of extrapulmonary tuberculosis may be limited by the relative inaccessibility of the sites of disease. Thus, response to treatment often must be judged on the basis of clinical and radiographic findings.

The use of adjunctive therapies such as surgery and corticosteroids is more commonly required in extrapulmonary tuberculosis than in pulmonary disease. Surgery may be necessary to obtain specimens for diagnosis and to treat such processes as constrictive pericarditis and spinal cord compression from Pott's Disease. Corticosteroids have been shown to be of benefit in preventing cardiac constriction from tuberculous pericarditis (43) and in decreasing the neurologic sequelae of all stages of tuberculous meningitis, especially when administered early in the course of disease (44).

Pregnancy and Lactation

Untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus than does treatment of the disease (45). However, tuberculosis during pregnancy is not an indication for therapeutic abortion. In a pregnant woman with tuberculosis it is essential that effective therapy be given. The initial treatment regimen should consist of isoniazid and rifampin. Ethambutol should be included unless primary isoniazid resistance is unlikely. Although the routine use of pyrazinamide in pregnancy is recommended by international tuberculosis organizations, recommendations for its general use in pregnancy in the United States cannot be made because of inadequate teratogenicity data.

Isoniazid, rifampin, and ethambutol all cross the placenta, but these drugs have not been demonstrated to have teratogenic effects. Pyridoxine is recommended for pregnant woman receiving isoniazid. Streptomycin, the only antituberculosis drug documented to have harmful effects on the fetus, interferes with development of the ear and may cause congenital deafness. This toxic potential is presumably shared by kanamycin and capreomycin; however, there is little specific information on the fetal effects of these two drugs. There is not enough information to determine the risk of cycloserine or ethionamide; they should be avoided if possible.

Because the small concentrations of antituberculosis drugs in breast milk do not produce toxicity in the nursing newborn, breast feeding should not be discouraged; conversely, drugs in breast milk should not be considered to serve as effective treatment for disease or as preventive treatment in a nursing infant (46).

Associated Disorders

Tuberculosis commonly occurs in association with other disease processes. An associated disorder may alter immune responsiveness, thereby predisposing a person to tuberculosis, or simply may be an illness that occurs frequently in the same social and cultural milieu as tuberculosis. Examples of the former class of disorders include HIV infection, hematologic or reticuloendothelial malignancies, immunosuppressive therapy, chronic renal failure, and malnutrition. Silicosis, by impairing pulmonary macrophage function, is a unique example of local immune dysfunction; treatment of culture-positive silicotuberculosis requires that the usual therapy be extended by at least 2 mo (47).

The latter group of disorders includes chronic alcoholism and its secondary effects. All of these conditions may influence the outcome of therapy. The response of the impaired host to treatment may not be as satisfactory as that of a person with normal host responsiveness. For this reason, therapeutic decisions for the impaired host must be individualized and steps taken when possible to try to correct the immune deficiency.

In patients with impairment of renal function, streptomycin, kanamycin, and capreomycin should be avoided if possible. If there is severe impairment of renal function, administration of drugs at more widely spaced intervals might be necessary, and measurement of blood concentrations might be helpful in adjusting dosage (48). Liver disease, particularly alcoholic hepatitis and cirrhosis, is commonly associated with tuberculosis. In one study,

the complications of potentially hepatotoxic antituberculosis drugs were not found to be greater in patients with liver disease (49). However, detecting such adverse effects if they occur may be difficult because of the preexisting disorder of hepatic function. In such patients, routine monitoring of liver function should be performed. In patients with neuropsychiatric disorders, directly observed therapy is recommended.

TREATMENT OF TUBERCULOSIS INFECTION

Preventive therapy presumably acts by diminishing or eradicating the bacterial population in "healed" or radiographically invisible lesions. Follow-up studies have demonstrated that the beneficial effect of 12 mo of isoniazid preventive therapy given to persons with a positive tuberculin skin test reaction persists for as long as 20 yr (50). Presumably, in the absence of reinfection, this protection persists for life.

Sometimes isoniazid is given to persons who are exposed to tuberculosis but not yet infected in an attempt to prevent the establishment of tuberculosis infection (primary prophylaxis). In this situation isoniazid is protective only while the person is receiving the drug.

Although isoniazid is usually safe, it is occasionally associated with adverse reactions. The most significant of these is hepatitis. Elevation of serum aminotransferase (transaminase) activity, probably reflecting mild hepatic injury, occurs in 10 to 20% of persons receiving isoniazid (51). This type of abnormality usually occurs within the first 6 mo of treatment, but it can occur at any time during therapy. In most persons, enzyme levels return to normal despite continuation of medication. However, progressive liver damage and clinical hepatitis may occur. The frequency of progressive liver damage generally increases with age. Drinking alcohol, especially on a daily basis, may enhance the risk of isoniazid-associated hepatitis. Fatal hepatitis associated with isoniazid has been reported. A recent report suggests that this risk is greatest among women, particularly black and Hispanic women (52). The risk may also be increased during the postpartum period.

PERSONS FOR WHOM PREVENTIVE THERAPY IS RECOMMENDED

Priorities for preventive therapy take into consideration the risk of developing tuberculosis compared with the risk of isoniazid toxicity (53). Recommendations for the use of isoniazid are based on a comparison of the risk of hepatic injury during the period of treatment with the potential lifelong benefit of preventive therapy. Also of importance is the benefit to society derived from preventive therapy because prevention of tuberculosis precludes the spread of new infection.

The appropriate criterion for defining a positive skin test reaction depends on the likelihood of tuberculosis infection and the risk of tuberculosis if infection has occurred (54). For persons with HIV infection, close contacts of infectious cases, and those with fibrotic lesions on chest radiograph, a reaction of $\geq$ 5 mm is considered positive. For other at-risk persons, including infants and children younger than 4 yr of age, a reaction of $\geq$ 10 mm is positive. Persons who are not likely to be infected with *M. tuberculosis* should generally not be skin tested because the predicted value of a positive skin test in low risk populations is poor. If a skin test is performed on a person who is not in a high risk category or who is not exposed to a high risk environment, a cutoff point of $\geq$ 15 mm is positive.

The following persons with positive tuberculin skin tests (as defined above) should be considered for isoniazid preventive therapy regardless of age.

1. *Persons with HIV infection and persons with risk factors for HIV infection whose HIV infection status is unknown but who are suspected of having HIV infection.* The risk of tuberculosis in a tuberculin-positive person with HIV infection may be as high as 6% per year (55). Thus, the identification of persons with dual infection and the administration of preventive therapy to these persons is of great importance. In addition, preventive therapy may be considered for HIV-infected persons who are tuberculin-negative but belong to groups in which the prevalence of tuberculosis infection is high (56).

2. Close *contacts of persons with newly diagnosed infectious tuberculosis.* Because persons in this group are likely to have been recently infected by the index case, their risk of developing tuberculosis will be relatively high, approximately 2 to 4% for the first year, with persons who have a positive tuberculin skin test having the greatest risk. The risk for very young children and adolescents may be as much as twice the adult risk. Furthermore, persons who do not develop disease in the period immediately following infection are at some risk of doing so for the remainder of their lives. In addition, tuberculin-negative (< 5 mm) children and adolescents who have been close contacts of infectious persons within the past 3 mo are candidates for preventive therapy until a repeat tuberculin skin test is done 12 wk after last contact with the infectious source. If the repeat skin test is positive ($\geq$ 5 mm), therapy should be continued. If the reaction remains negative, therapy need not be continued unless there is continuing exposure to an infectious source case. If preventive therapy is not prescribed initially, the tuberculin skin test should be repeated in 3 mo and preventive therapy prescribed at that time if skin test conversion has occurred and the chest radiograph remains negative.

3. *Recent tuberculin skin test converters ($\geq$ 10 mm increase within a 2-yr period for those < 35 yr of age; $\geq$ 15 mm increase for those $\geq$ 35 yr of age).* All infants and children younger than 4 yr of age with a $\geq$ 10 mm skin test are included in this category. The excess risk of developing tuberculosis is concentrated in the first 1 to 2 yr after infection.

4. *Persons with medical conditions that have been reported to increase the risk of tuberculosis.* Persons in the following groups are generally considered at increased risk of developing tuberculosis, if infected (57). In most instances the risk is not well quantitated and probably varies from person to person.

(1) *Diabetes mellitus.* The risk for this group may be two to four times that of the general population. Particularly at risk are poorly controlled insulin-dependent diabetics.

(2) *Prolonged therapy with adrenocorticosteroids.* The exact risk of tuberculosis associated with corticosteroid therapy is unknown. However, tuberculosis that develops during corticosteroid therapy is more likely to be disseminated or to present in an obscure fashion. Because > 15 mg of prednisone (or equivalent) given daily for 2 to 3 wk markedly reduces tuberculin reactivity, this is probably the lower limit of corticosteroid dose associated with an increased risk of tuberculosis. There are insufficient data at present to categorically recommend isoniazid preventive therapy for persons treated with < 15 mg prednisone daily(or its equivalent) or with alternate-day corticosteroids. However, because long-term corticosteroid requirements are unpredictable, and because the frequency of isoniazid-associated hepatitis increases with age, it may be prudent to consider some of these persons for preventive therapy.

(3) *Immunosuppressive therapy* Similar to those receiving corticosteroids, persons receiving other forms of immunosuppressive therapy are at increased risk of tuberculosis.

(4) *Some hematologic and reticuloendothelial diseases, such*

as leukemia or Hodgkin's disease. These conditions may be associated with suppressed cellular immunity and an increased risk of tuberculosis.

(5) *Injection drug users known to be HIV-seronegative.* Through unknown mechanisms, persons injecting illicit drugs may be at increased risk of tuberculosis even if not infected with HIV.

(6) *End-stage renaldisease.* Persons with end-stage renal disease are at increased risk of developing tuberculosis and appear particularly predisposed to developing extrapulmonary and disseminated disease. Because many of these patients will be anergic, a documented history of a prior significant tuberculin skin test is an indication for preventive therapy unless the person has been treated previously.

(7) *Clinical situations associated with substantial rapid weight loss or chronic undernutrition.* These situations include: intestinal bypass surgery for obesity, which appears to carry an increased risk particularly for extrapulmonary tuberculosis; the postgastrectomy state; chronic peptic ulcer disease; chronic malabsorption syndromes; chronic alcoholism; and carcinomas of the oropharynx and upper gastrointestinal tract that prevent adequate nutritional intake. The postgastrectomy state may increase the risk of developing tuberculosis even without weight loss.

In addition, even in the absence of any of the above risk factors, persons < 35 yr of age in the following high-incidence groups are appropriate candidates for preventive therapy if their skin test is positive (≥ 10 mm).

1. *Foreign-born persons from high-prevalence countries.* These countries include those in Latin America, Asia, and Africa that have a high incidence of tuberculosis.

2. *Medically underserved low-income populations, including high-risk racial or ethnic minority populations, especially blacks, Hispanics, and Native Americans.*

3. Residents of facilities for long-term care (e.g., correctional institutions, nursing homes, and mental institutions).

The staff of facilities in which an individual with current tuberculosis would pose a risk to large numbers of susceptible persons (e.g., correctional institutions, nursing homes, mental institutions, other health-care facilities, schools, and child-care facilities) may also be considered for preventive therapy if their tuberculin reaction is ≥ 10 mm induration.

Persons younger than 35 yr of age with none of the above risk factors who have a positive skin test (≥ 15 mm) may also be considered for preventive therapy based on individual assessment of risk and benefits.

SCREENING PROCEDURES

Before isoniazid preventive therapy is started for any of the above indications, it is important to undertake the following evaluations.

1. Exclude bacteriologically positive or radiographically progressive tuberculosis. Every person who has a significant tuberculin skin test reaction should have a chest radiograph. If there are findings consistent with pulmonary tuberculosis, further studies, including medical evaluation, bacteriologic examinations, and comparison of the current and old radiographs, should be made to exclude progressive disease. Appropriate evaluation should be performed if extrapulmonary tuberculosis is suspected. Because of the risk of inducing isoniazid resistance when isoniazid is used alone in a person with current tuberculosis, the recommended regimens for treatment of disease should be used until the diagnosis is clarified. If the evaluation confirms previous (not current) tuberculosis, therapy of multidrug treatment may be stopped after 4 mo in adults and after 6 mo in children (32).

2. Question for a history of therapy or preventive therapy for tuberculosis to exclude those who have been adequately treated.

3. Question for a history of prior isoniazid preventive therapy to exclude those who have had an adequate course of the drug.

4. Check for contraindications to the administration of isoniazid for preventive therapy. These include: (7) Previous isoniazid-associated hepatic injury. (2) History of severe adverse reactions to isoniazid such as drug fever, rash, and arthritis. (3) Acute or unstable liver disease of any etiology. Hepatitis B surface antigen positivity per se is not a contraindication.

5. Identify patients for whom special precautions are indicated. These include: (7) Age greater than 35 yr. (2) Concurrent use of any other medication on a long-term basis (in view of possible drug interactions). (3) Daily use of alcohol, which may be associated with a higher incidence of isoniazid-associated hepatitis. (4) History of previous discontinuation of isoniazid because of possible, but not definite, related side effects, e.g., headaches, dizziness, nausea. (5) Current chronic liver disease. (6) Existence of peripheral neuropathy or of a condition such as diabetes mellitus or alcoholism that might predispose to the development of neuropathy. (7) Pregnancy. Although no harmful effects of isoniazid to the fetus have been observed, preventive therapy generally should be delayed until after delivery. There does not appear to be any substantial increase in tuberculosis risk for women as a result of pregnancy. However, for pregnant women likely to have been recently infected or with high-risk medical conditions, especially HIV infection, isoniazid preventive therapy should begin when the infection is documented. (8) Injection drug use. (9) A recent report suggests an increased risk of fatal hepatitis associated with isoniazid among women, particularly black and Hispanic women (52). The risk may also be increased during the postpartum period.

ADMINISTRATION OF ISONIAZID PREVENTIVE THERAPY

lsoniazid is used alone for preventive therapy. The drug is given in a single daily dose of 300 mg/d for adults and 10 to 15 mg/kg body weight/d, not to exceed 300 mg/d, for children. It is recommended to dispense isoniazid only in monthly allotments. In most clinical trials of isoniazid the drug has been given for 12 mo, but there is good evidence to suggest that 6 mo of preventive therapy confers a nearly comparable degree of protection (56, 59). Durations of less than 6 mo have been shown to be substantially less effective than 6 mo of therapy, and those of longer than 1 yr do not provide additional benefit. There are no data on the effectiveness of 9 mo of preventive therapy, but presumably it is intermediate between the effectiveness of 6- and 12-mo regimens. Every effort should be made to ensure adherence to preventive therapy for at least 6 mo. Persons with HIV infection should receive 12 mo of therapy. The American Academy of Pediatrics recommends that children receive 9 mo of preventive therapy (36).

For persons at especially high risk of tuberculosis whose adherence is questionable, directly observed preventive therapy may be indicated. When resources do not permit directly observed daily therapy, isoniazid may be given twice weekly at the dose of 15 mg/kg. Although there are limited data on intermittent isoniazid preventive therapy, results of chemotherapy studies in which isoniazid is given twice weekly in the sterilizing phase of treatment suggest that this would be an effective form of preventive therapy in both adults and children.

MONITORING PREVENTIVE THERAPY

The person receiving preventive therapy or a responsible adult in a household with children receiving preventive therapy should be questioned carefully at monthly intervals for symptoms or signs consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever of greater than 3 d duration, and/or abdominal tenderness (especially right upper quadrant discomfort).

If any of these or other signs or symptoms occur during preventive therapy, patients should be advised to report immediately to the clinic or health-care provider for evaluation, including biochemical tests for hepatitis. The use of a standardized form for interviewing will help ensure alertness to all signs and symptoms, expedite the interview process, and provide for standardized data collection.

As noted, 10 to 20% of those receiving isoniazid will develop some mild abnormality of liver function (an elevated aspartate aminotransferase). These abnormalities tend to resolve even if isoniazid is continued. Because there is a higher frequency of isoniazid-associated hepatitis among persons older than 35 yr of age, a transaminase measurement should be obtained prior to the starting and monthly during the course of preventive therapy in this age group. Other factors associated with an increased risk of hepatitis include daily use of alcohol, chronic liver disease, and injection drug use. There is also evidence to suggest that postpubertal black and Hispanic women are at greater risk for hepatitis or drug interactions. More careful monitoring should be considered in these groups, possibly including more frequent laboratory monitoring. If any of these tests exceeds three to five times the upper limit of normal, discontinuation of isoniazid should be strongly considered. Liver function tests are not a substitute for a clinical evaluation at monthly intervals or for the prompt assessment of signs or symptoms of adverse reactions occurring between regularly scheduled evaluations.

ALTERNATIVE FORMS OF TUBERCULOSIS PREVENTION

There are occasional situations in which alternative forms of preventive therapy might be desirable (60). Although other drugs might also be effective for preventive therapy, there are currently no data available documenting the clinical efficacy of any drug other than isoniazid.

Management of Close Contacts of Isoniazid-resistant Cases

In the situation where there is confidence that the source case has isoniazid-resistant organisms, it appears reasonable to treat child contacts and those adult contacts who appear particularly susceptible to tuberculosis (e.g., immunocompromised hosts) with rifampin. Some clinicians would add a second drug such as ethambutol to which the organism is believed susceptible. The drug(s) should be given in standard therapeutic doses for 6 mo; a 9-mo treatment period for children is recommended. In situations in which there is less confidence that the infection is due to isoniazid-resistant organisms, isoniazid should be used.

Management of Persons with a High Probability of Infection with Multidrug-Resistant Organisms

In persons likely to have been infected with bacilli resistant to both isoniazid and rifampin, observation without preventive therapy has usually been recommended because no other drugs have been evaluated for preventive therapy. However, in persons with an especially high risk of tuberculosis (e.g., persons with HIV infection), preventive therapy should be considered (61). If the organisms are thought to be susceptible, 6 mo of daily ethambutol and pyrazinamide at the usual therapeutic doses may be considered. If infection is due to organisms resistant to ethambutol as well, the combination of pyrazinamide plus a quinolone (ofloxacin or ciprofloxacin) for 6 mo is recommended. Careful assessment to exclude active tuberculosis prior to the initiation of preventive therapy is mandatory.

Management of Persons Intolerant to Isoniazid

An approach similar to that taken for contacts of isoniazid-resistant cases can be used here with the exception that isoniazid is not one of the alternatives.

Use of BCG

Bacille Calmette Guérin (BCG) was derived from a strain of *M. bovis* attenuated through years of serial passage in culture at the Pasteur Institute in Lille, France. There are many BCG vaccines available, most of which have not been recently studied. The protection obtained from studies of previous vaccines has varied from zero to 80% (62). The most recent large trial, conducted in South India, failed to show a protective effect despite the fact that the vaccines used were believed to be two of the most potent available (63). Subsequently, however, a large number of nonrandomized studies (case-control and cohort studies) have suggested that BCG vaccine does protect infants and young children from the more serious forms of tuberculosis, although the ability of BCG to prevent adult forms of tuberculosis remains questionable (64).

Even if vaccines of proved efficacy and safety were available, the potential benefit of BCG vaccination in a nation such as the United States would be small because most tuberculosis occurs in persons who have already been infected. Such persons will not benefit from BCG.

BCG rarely causes serious complications; osteomyelitis and death from disseminated BCG infection have occurred in only one case per million doses administered. The frequency of side effects, most commonly prolonged ulceration and local adenitis, occur in 1 to 10% of vaccines, varying with the vaccine used, the intensity with which adverse reactions are sought, and the population vaccinated. BCG vaccination may cause tuberculin skin test conversion, thus rendering the test less useful.

Because of these shortcomings, BCG is recommended only in the following situations (64).

1. BCG vaccine is strongly recommended for infants and children with negative tuberculin skin tests who: (7) are at high risk of intimate and prolonged exposure to persistently untreated or ineffectively treated patients with infectious pulmonary tuberculosis, cannot be removed from the source of exposure, and cannot be placed on long-term preventive therapy, or (2) are continuously exposed to persons with tuberculosis who have bacilli resistant to both isoniazid and rifampin.

2. BCG vaccination is also recommended for tuberculin-negative infants and children in groups in which the rate of new infections exceeds 1% per year and for whom the usual surveillance and treatment programs have been attempted but are not operationally feasible. These groups include persons without regular access to health care, those for whom usual health care is culturally or socially unacceptable, or groups who have demonstrated an inability to effectively use existing accessible care. In view of the recent outbreaks of multidrug-resistant tuberculosis, these recommendations are currently under review.

Vaccination should be administered only by the route indicated in the package labeling and only in the suggested dose. If a newborn is vaccinated, one half the usual dose should be used.

Depressed host immunity (from illness such as HIV infection or therapy with immunosuppressive drugs) is a contraindication to BCG administration.

This statement was prepared by an Ad Hoc Committee of the Scientific Assembly on Microbiology, Tuberculosis, and Pulmonary Infections. Members of the Committee were:

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