Chemotherapy for Tuberculosis in Infants and Children

Committee on Infectious Diseases

Active tuberculosis is diagnosed in more than 1100 children annually in the United States. The therapy for patients with tuberculosis has undergone major changes during the past decade, including demonstration of the efficacy of multidrug, short-course chemotherapy for pulmonary tuberculosis in adults. At least nine studies of 6-month antituberculosis chemotherapy have demonstrated comparable results in children. The purpose of this statement is to give revised recommendations for treatment of tuberculosis in infants and children. These recommendations have been formulated in collaboration with the Division of Tuberculosis Elimination of the Centers for Disease Control and the American Thoracic Society.

MICROBIOLOGIC RATIONALE FOR TREATMENT

Laboratory observations of Mycobacterium tuberculosis and clinical therapy trials have led to a hypothesis concerning the populations of tubercle bacilli and the actions of various antimycobacterial drugs and drug combinations. Mycobacteria replicate slowly, can remain dormant for prolonged periods, and can be killed by drugs only during replication. In the host, bacilli live in several sites: open cavities, closed caseous lesions, and within macrophages. Each site contains bacilli with a different population size, metabolic activity, and rate of replication. Open cavities, which are rare in infants and children, have the largest number of mycobacteria. Naturally occurring drug-resistant mutants of M tuberculosis occur within large bacterial populations even before chemotherapy is started. The number of drug-resistant mutants is proportional to the size of the mycobacterial population; thus, they are common in open cavities, but less common in caseous lesions and within macrophages. Mutants naturally resistant to two drugs are virtually nonexistent.

The various antituberculosis drugs differ in their actions and primary sites of activity. Isoniazid and rifampin are bactericidal against all populations of mycobacteria. Streptomycin is most active against M tuberculosis in open cavities, while pyrazinamide may contribute to killing organisms within macrophages. Other drugs, including ethambutol, ethionamide, and p-aminosalicylic acid, prevent replication of mycobacteria but do not readily kill the organisms. The earliest treatment regimens for tuberculosis combined the actions of a bactericidal drug such as isoniazid and/or streptomycin with a bacteriostatic drug that suppressed emergence of drug-resistant mutants. Microbiologic cure required 18 to 24 months of treatment. Current chemotherapy using at least two bactericidal drugs to which the isolate is susceptible usually can effect a cure in 6 to 9 months.

RECENT CLINICAL TRIALS

Nine months of therapy with isoniazid and rifampin will cure virtually 100% of adults and children with drug-susceptible pulmonary tuberculosis. The drugs are given daily for the first 1 to 2 months, and for the remaining time can be given daily or twice weekly with equivalent results and rates of adverse reactions. The success of twice weekly therapy allows direct observation of drug administration by a health care professional in cases of suspected or proven noncompliance. While trials for most forms of tuberculosis in adults and children using only isoniazid and rifampin have evaluated therapy of 9 months duration, hilar adenopathy in children has been treated successfully with only 6 months of this combination.

Adults with pulmonary tuberculosis are treated successfully with a 6-month regimen of isoniazid, rifampin, and pyrazinamide daily for the first 1 to 2 months, followed by isoniazid and rifampin daily or twice weekly for 4 to 5 months. The nine published pediatric studies of 6-month therapy for pulmonary tuberculosis have included more than 1500 children and used slightly different regimens, all containing at least three drugs in the initial phase of treatment, usually isoniazid, rifampin, and pyrazinamide. Giving directly observed medications twice weekly during the continuation phase was as effective and safe as daily self-administration. Two studies using intermittent therapy for the entire 6 months yielded success rates equivalent to the studies in which therapy was initially given daily. In several studies, success was <95%, but for all studies combined it was >95%.

The three major antituberculosis drugs, isoniazid, rifampin, and pyrazinamide, achieve tissue and body fluid concentrations adequate to kill M tuberculosis in all body sites. Although fewer studies of treatment of drug-susceptible extrapulmonary tuberculosis have been reported, infection in most sites is treated adequately by 9 months of isoniazid and rifampin or 6-month regimens using isoniazid, rifampin, and pyrazinamide for 2 months, followed by isoniazid and rifampin for 4 months. Bone or joint tuberculosis
occasionally requires longer durations of therapy. Treatment of tuberculous meningitis with isoniazid and rifampin for 12 months is well established, but durations of 6 to 9 months using four drugs (usually isoniazid, rifampin, pyrazinamide, and streptomycin) in the initial phase also appear to be effective.\textsuperscript{18}

Adjunct treatment of certain forms of tuberculosis with corticosteroids has been considered controversial. Corticosteroids have been used for therapy of tuberculous meningitis to reduce vasculitis, inflammation, and ultimately, intracranial pressure.\textsuperscript{19} A recent study demonstrated lower rates of mortality and long-term neurologic sequelae among patients with tuberculous meningitis treated with corticosteroids compared with nonsteroid-treated controls.\textsuperscript{20} Controlled trials have demonstrated beneficial effects of corticosteroids for patients with endobronchial primary tuberculosis,\textsuperscript{21} pleural effusion with mediastinal shift,\textsuperscript{22} and pericardial effusion.\textsuperscript{23}

**DRUG RESISTANCE**

The incidence of drug-resistant tuberculosis is increasing in many parts of the United States and throughout the world. The three major factors that contribute to the emergence of drug resistance are as follows: 1) the use of antituberculosis medications in uncontrolled over-the-counter preparations available in many foreign countries; 2) poor compliance by patients; and 3) improper treatment by physicians, most commonly the failure to employ an adequate antituberculosis regimen at the beginning of therapy. Regimens for drug-resistant tuberculosis must include at least two bactericidal drugs to which the isolate is susceptible. Primary resistance to streptomycin or isoniazid is most common. Primary resistance to rifampin or pyrazinamide remains rare, but pyrazinamide may not effectively prevent the emergence of rifampin resistance during therapy when primary isoniazid resistance is also present. A fourth drug, usually ethambutol, should be added to the initial regimen when the patient is at increased risk for primary isoniazid resistance.

**COMPLIANCE**

Noncompliance is a major problem in tuberculosis control due to the long-term nature of treatment.\textsuperscript{24} As treatment regimens become shorter in duration, compliance assumes an even greater importance. Suspected cases of tuberculosis must be reported to the local health department so it can compile accurate statistics, perform necessary contact investigations, and assist both patients and health care providers in overcoming barriers to compliance. To comply, the patient and family must know what is expected of them through verbal and written instructions in the patient's main language. Appointment reminders, both by postcard and telephone, are helpful. An assessment of potential noncompliance should be made at the initiation of therapy. Missed appointments should be brought quickly to the attention of the responsible public health officials who may be able to use incentives/enablers, behavior modification, or even confinement to ensure compliance. If the physician suspects any chance of noncompliance with daily self-administered medications, directly observed therapy should be instituted.

**RECOMMENDATIONS**

See Tables 1, 2, and 3 for Summary and Drug Doses

1. For drug-susceptible pulmonary tuberculosis, the Academy recommends as standard therapy a 6-month regimen using isoniazid, rifampin, and pyrazinamide daily for 2 months, followed by isoniazid and rifampin given daily or twice weekly for 4 months. Twice-weekly drug administration should be directly observed by a health care professional, i.e., the professional is present when the medication is administered.

An alternative in areas where the incidence of drug resistance is low is a 9-month regimen of isoniazid and rifampin given daily for 1 month, then daily or twice weekly for 8 months.

2. If any doubt exists about the reliability of self-administered daily medication, directly observed twice-weekly therapy administered by an employee of the local health department or other health care professional should be given. When social or other constraints prevent reliable daily self-administration of drugs in the initial phase, drugs can be given two or three times per week from the beginning under direct observation. The optimal duration of therapy given in this manner is not firmly established, but durations of 6 to 9 months are generally successful for pulmonary tuberculosis and hilar adenopathy.

3. In general, the treatment of hilar adenopathy should be the same as that for pulmonary tuberculosis. However, when drug resistance is unlikely, a 6-month regimen of isoniazid and rifampin is usually sufficient. Because hilar adenopathy frequently requires 2 to 3 years for complete radiographic resolution, a normal chest radiograph is not a necessary criterion for discontinuation of antituberculosis medications in children.

4. In most cases, 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; data are inadequate at present to support 6-month therapy for these conditions.

For tuberculous meningitis, the Academy recommends a 12-month regimen using initial daily treatment with isoniazid, rifampin, pyrazinamide, and streptomycin for 2 months, followed by isoniazid and rifampin administered daily or twice weekly under direct observation for 10 months. Based on personal experience and as yet unpublished data, some experts recommend a treatment duration of 6 to 9 months. Four drugs are used initially to ensure adequate therapy even if unsuspected drug resistance is present. For non-central nervous system extrapulmonary tuberculosis, ethambutol can be used instead of streptomycin if the risk of drug resistance is significant.

5. For all cases of childhood tuberculosis, drug susceptibility information should be sought from the adult source case and/or the child and should be used to determine appropriate therapy. Drug-resistant tuberculosis is an increasing problem and is more likely...
TABLE 1. Recommended Treatment Regimens for Tuberculosis in Infants, Children, and Adolescents

<table>
<thead>
<tr>
<th>Tuberculous Infection/Disease</th>
<th>Regimens*</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic infection (positive skin test, no disease)</td>
<td>9 mo of I, 9 mo of R</td>
<td>• At least 6 consecutive mo of therapy with good compliance should be given.</td>
</tr>
<tr>
<td>Isoniazid susceptible Pulmonary</td>
<td>1. 6-mo (standard). 2 mo of I, R, &amp; Z daily, followed by 4 mo of I &amp; R daily or 2 mo of I, R, &amp; Z daily, followed by 4 mo of I &amp; R twice weekly, directly observed</td>
<td>• If drug resistance is possible, especially for the 9-mo regimen, an additional drug (ethambutol or streptomycin) should be added to the initial therapy until drug susceptibility is determined.</td>
</tr>
<tr>
<td>Isoniazid resistant Pulmonary</td>
<td>2. 9-mo (alternative). 9 mo of I &amp; R daily or 1 mo of I &amp; R daily followed by 8 mo of I &amp; R twice weekly, directly observed</td>
<td>• Drugs can be given two or three times per week under direct observation in the initial phase if noncompliance is likely.</td>
</tr>
<tr>
<td>Hilar adenopathy</td>
<td>Same as Pulmonary</td>
<td>• See Pulmonary.</td>
</tr>
<tr>
<td>Meningitis, disseminated (miliary) and bone/joint</td>
<td>2 mo of I, R, Z &amp; S daily, followed by 10 mo of I &amp; R daily or 2 mo of I, R, Z &amp; S daily, followed by 10 mo of I &amp; R twice weekly, directly observed</td>
<td>• Streptomycin used in initial therapy until drug susceptibility is known.</td>
</tr>
<tr>
<td>Extrapulmonary other than meningitis, disseminated (miliary) or bone/joint</td>
<td>Same as Pulmonary</td>
<td>• For patients who may have acquired tuberculosis in geographic locales where resistance to streptomycin is common, capreomycin (15–30 mg/kg/d) or kanamycin (15–30 mg/kg/d) may be used instead of streptomycin.</td>
</tr>
</tbody>
</table>

* I = isoniazid; R = rifampin; Z = pyrazinamide; S = streptomycin.

TABLE 2. Commonly Used Drugs for the Treatment of Tuberculosis in Infants, Children, and Adolescents

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dosage Forms</th>
<th>Daily Dose, mg/kg/d</th>
<th>Twice-Weekly Dose, mg/kg/dose</th>
<th>Maximum Dose</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid*</td>
<td>Scored tablets: 100 mg 300 mg Syrup: 10 mg/mL†</td>
<td>10–15†</td>
<td>20–40</td>
<td>Daily: 300 mg Twice weekly: 900 mg</td>
<td>Mild hepatic enzyme elevation, hepatitis, peripheral neuritis, hypersensitivity</td>
</tr>
<tr>
<td>Rifampin*</td>
<td>Capsules: 150 mg 300 mg Syrup: formulated in syrup from capsules§</td>
<td>10–20</td>
<td>10–20</td>
<td>600 mg</td>
<td>Orange discoloration of secretions/urine, staining contact lenses, vomiting, hepatitis, flu-like reaction, thrombocytopenia, may render birth-control pills ineffective</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Scored tablets: 500 mg</td>
<td>20–40</td>
<td>50–70</td>
<td>2 g</td>
<td>Hepatotoxicity, hyperuricemia</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Vials: 1 g, 4 g</td>
<td>20–40 (IM)¶</td>
<td>20–40 (IM)</td>
<td>1 g</td>
<td>Ototoxicity, nephrotoxicity, skin rash</td>
</tr>
<tr>
<td>Ethambutol¶</td>
<td>Tablets: 100 mg 400 mg</td>
<td>15–25</td>
<td>50</td>
<td>2.5 g</td>
<td>Optic neuritis (reversible), decreased visual acuity, decreased red-green color discrimination, gastrointestinal disturbance, hypersensitivity</td>
</tr>
</tbody>
</table>

* Rifamate is a capsule containing 150 mg of isoniazid and 300 mg of rifampin. Two capsules provide the usual adult (>50 kg) daily doses of each drug.
† When isoniazid is used in combination with rifampin, the incidence of hepatotoxicity increases if the isoniazid dose exceeds 10 mg/kg/d.
‡ Many experts recommend not using isoniazid syrup, because it is unstable and is associated with frequent gastrointestinal complaints, especially diarrhea.
§ Some experts recommend not using rifampin syrup because of instability.
¶ Ethambutol is probably safe in young children, but should be used with caution when monitoring visual acuity or color discrimination is difficult.
¶ IM = intramuscular.

To occur in certain regions of the United States and among the following groups: foreign-born individuals from high-risk areas of Asia, Africa, and Latin America; the homeless; persons previously treated for tuberculosis; and children with tuberculosis whose adult source case is in one of the aforementioned groups. If the child is at risk for drug resistance, streptomycin or ethambutol should be added to the initial phase of all regimens until drug susceptibilities are known. In cases of tuberculosis with isoniazid or rifampin resistance, standard short-course chemotherapy is not recommended.

6. Optimal therapy of tuberculosis in children with human immunodeficiency virus (HIV) infection is not
TABLE 3. Summary of Drug Doses

<table>
<thead>
<tr>
<th>Child's Weight</th>
<th>Isoniazid</th>
<th>Rifampin</th>
<th>Pyrazinamide</th>
<th>Ethambutol</th>
</tr>
</thead>
<tbody>
<tr>
<td>lb</td>
<td>kg</td>
<td>Dose offered, mg</td>
<td>Resulting dose, mg/kg/d</td>
<td>Dose offered, mg</td>
</tr>
<tr>
<td>15-21</td>
<td>6-9.5</td>
<td>100</td>
<td>11-17</td>
<td>150</td>
</tr>
<tr>
<td>30-40</td>
<td>14-18</td>
<td>200</td>
<td>11-14</td>
<td>300</td>
</tr>
<tr>
<td>41-51</td>
<td>19-23</td>
<td>250</td>
<td>11-13</td>
<td>300</td>
</tr>
<tr>
<td>52-62</td>
<td>23.5-28</td>
<td>300</td>
<td>11-13</td>
<td>300</td>
</tr>
<tr>
<td>63-78</td>
<td>28.5-35</td>
<td>300</td>
<td>9-11</td>
<td>450</td>
</tr>
<tr>
<td>79-89</td>
<td>35.5-40</td>
<td>300</td>
<td>&lt;10</td>
<td>450</td>
</tr>
<tr>
<td>90-100</td>
<td>40.5-45</td>
<td>300</td>
<td>&lt;10</td>
<td>600</td>
</tr>
<tr>
<td>100+</td>
<td>46+</td>
<td>300</td>
<td>&lt;10</td>
<td>600</td>
</tr>
</tbody>
</table>


yet established. Most HIV-infected adults with tuberculosis respond well to antituberculosis drugs but may require longer duration of treatment.\textsubscript{25,26} Therapy always should include at least three drugs initially and should be continued for at least 9 months. HIV testing (with informed consent) is recommended for infants and children with tuberculosis disease, especially those with risk factors for HIV infection. Culture confirmation and drug susceptibility patterns from the child should be sought vigorously.

7. Because rates of adverse reactions to antituberculosis medications are low in infants and children, routine laboratory monitoring of blood counts, liver function tests, and serum uric acid is usually not necessary. Physician-patient contact at monthly intervals is important to assess toxicity, compliance, and effectiveness. In cases of severe tuberculosis, especially meningitis and disseminated disease, the incidence of hepatotoxic reactions to antituberculosis drugs is higher, and results of liver function tests should be monitored during the first several months of treatment.\textsuperscript{27,28}

8. The Academy recommends a 9-month regimen of isoniazid for children with asymptomatic tuberculous infection (i.e., those with a positive tuberculin skin test and no evidence of disease). For adults with asymptomatic infection, isoniazid alone for 6 to 12 months has been demonstrated to be highly effective in preventing the development of tuberculous disease. Rifampin given for 9 months is recommended for children with isoniazid-resistant infection, such as those whose source has been proven microbiologically to be excreting isoniazid-resistant organisms. Although controlled trials have not been reported, either drug can be given twice weekly under direct observation when compliance with daily self-administered therapy cannot be ensured.

9. Administration of pyridoxine is not generally necessary for children taking isoniazid, because peripheral neuritis or convulsions caused by inhibition of pyridoxine metabolism are extremely rare. However, pyridoxine supplements are recommended for children or adolescents on meat- or milk-deficient diets, malnourished children, breast-feeding infants, and pregnant women.

10. The administration of corticosteroids should be considered in cases of tuberculous meningitis. Most commonly, corticosteroids are given daily for 4 to 6 weeks, then tapered during the next 2 to 3 weeks. Corticosteroids also may be considered in cases of pleural and pericardial effusions to hasten reabsorption of fluid, in severe miliary disease to mitigate alveolocapillary block, and in endobronchial disease to relieve obstruction and atelectasis. Corticosteroids should be given only when accompanied by adequate antituberculosis therapy.

11. Consultation with an expert in tuberculosis is recommended in the following situations: 1) cases of drug-resistant tuberculosis; 2) children with severe forms of tuberculosis in which therapy with corticosteroids may be indicated; and 3) the treatment of tuberculosis in pregnant women and HIV-infected children.

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