Treatment of Tuberculous Infection and Disease

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The key to the treatment of infections due to Mycobacterium tuberculosis is to supply the proper medications in proper doses for an appropriate amount of time. The number of medications and the duration of therapy are dictated by the extent of the infection. The medications are not effective, however, if they never enter the patient's body, so adherence to the prescribed therapy ultimately will be responsible for treatment success or failure. Clinicians delivering health care to children should be familiar with the proper approach to the treatment of tuberculous infection and disease.

BASIS FOR TREATMENT

The causative agent of tuberculosis, M. tuberculosis, is a slow-growing acid-fast bacillus that replicates well only in a highly aerobic environment with a neutral or alkaline pH. Although only susceptible to therapy during replication, the organism has the capacity of lying dormant for long periods of time. The numbers of organisms present will vary according to the type of disease affecting the patient. For instance, in cavitary lesions of the lung, large numbers of organisms are present (10^7 to 10^9) due to the inviting milieu. Caseous lesions of the lungs, which are more commonly found in children, have fewer organisms present (10^3 to 10^5), since the environment is less aerobic and, therefore, less hospitable.1

When treating tuberculous disease, it is always important to understand that, although the population of bacilli as a whole may be very susceptible to antituberculosis medications, there is always a subpopulation of organisms present that is resistant to specific antituberculosis agents.2 This naturally occurring resistance is present prior to any chemotherapy and is termed primary resistance. Secondary resistance is of greater concern and is due to partial or ineffective therapy. This type of resistance is on the increase in the United States due in part to individuals who were placed on inappropriate antituberculosis medications or who were not adherent to their treatment regimens.3

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TABLE 1  
Medications Used in the Treatment of Tuberculosis in Children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Availability</th>
<th>Daily Dose (mg/kg/day)</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Scored tablets (100/300 mg)</td>
<td>10-15</td>
<td>300 mg</td>
</tr>
<tr>
<td></td>
<td>Suspension (10 mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Capsules (150/300 mg)</td>
<td>10-20</td>
<td>600 mg</td>
</tr>
<tr>
<td></td>
<td>Formulated suspension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Scored tablets (500 mg)</td>
<td>20-40</td>
<td>2 g</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Vial (1.5 g)</td>
<td>20-40</td>
<td>1 g</td>
</tr>
<tr>
<td></td>
<td>Intramuscular injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Tablets (100/400 mg)</td>
<td>15-25</td>
<td>2.5 g</td>
</tr>
</tbody>
</table>

Due to the varying numbers of mycobacteria present and the concern about primary and secondary resistance, it is easy to understand why a single anti-tuberculosis agent should not be used to treat tuberculosis disease. The number of medications used, therefore, should be proportional to the number of mycobacteria present in the patient. Patients with pulmonary lesions (tuberculous disease) will have a large number of organisms and require two or more medications, whereas a patient with a positive tuberculin skin test and a normal chest roentgenogram (tuberculous infection) is infected with fewer organisms and can be treated with one medication.

CONSIDERATIONS FOR CHILDREN

The treatment of tuberculosis disease in children always has been based on regimens used to treat adults. Childhood tuberculosis, however, differs from adult disease in several ways that may affect therapy. Children do not typically develop cavitary lesions as part of their primary infection. Instead, they develop closed caseous lesions. Therefore, the number of infecting mycobacterial organisms is smaller and the risk of secondary resistance is less likely, even if adherence is poor.

Children younger than 4 years of age are more likely to develop extrapulmonary and disseminated forms of tuberculosis disease compared with adults. Due to these risk factors, it is important to treat children with medications that penetrate a wide variety of tissues, including the meninges. A thorough physical examination and laboratory evaluation will aid the clinician to further delineate the extent of extrapulmonary involvement. To avoid poor outcomes, however, it is always better to overestimate rather than underestimate the extent of tuberculosis disease.

Most commercially prepared dosage forms of anti-tuberculosis medications are made for adults. This leads to crushing pills or making suspensions from these preparations for children. This may directly affect both adherence to therapy and acceptance of medication by the child, since these preparations may not be palatable or well tolerated. In using these types of preparations, it is important to realize that children can tolerate larger doses per kilogram of body weight of the anti-tuberculosis medications with fewer side effects compared with adults. Children usually will achieve higher serum concentrations, but it is not known whether this has any therapeutic benefit. The higher serum concentrations do, however, place children at increased risk for serious hepatotoxic reactions if they are severely ill or malnourished.

ANTITUBERCULOSIS MEDICATIONS

Historically, combination therapy has been used with great success over the years to combat tuberculosis. Regimens such as isoniazid and streptomycin achieved microbiologic cure in 18 to 24 months. Adherence to such treatment protocols was poor, however, due to the prolonged duration of therapy. The recent addition of rifampin and pyrazinamide to treatment regimens has enabled the duration of therapy to be reduced significantly. With the addition of rifampin to regimens containing isoniazid and streptomycin, cure rates approaching 100% have been reported in patients with pulmonary tuberculosis after 9 months of therapy.

Today, the goal of therapy is to attack the bacillus with a combination of bactericidal medications that exert their effect in all of the organism's potential environments. With the use of such an intense regimen in the early treatment phase, the duration of therapy can be shortened successfully.

With such information, it is easy to understand why isoniazid, rifampin, and pyrazinamide have become the backbone of antituberculosis therapy. Streptomycin and ethambutol complete the arsenal of the most common antituberculosis medications used in children (Table 1). Although these medications are important, so is an understanding of how to use them. Treatment plans must include multiple drugs to which the organisms are susceptible, and the medications must be taken on a regular basis for a sufficient
period of time. The duration of treatment will be dictated by the extent of tuberculous disease, the adherence of the patient, and the response to treatment.

Isoniazid

Isoniazid is the most widely used antituberculosis medication. It is an ideal agent because it is bacterioidal, easily administered, and relatively nontoxic. Absorption from the gastrointestinal tract is almost complete if used in the appropriate preparation. Isoniazid penetrates into all body fluids and cavities producing levels similar to those found in the serum. For children, it is preferable to use the tablets instead of the commercially available suspension because the suspension may cause diarrhea. The tablets may be crushed and given with food. Isoniazid has been associated with symptomatic pyridoxine deficiency in adults, but rarely causes problems in children. Pyridoxine replacement, therefore, is not routinely indicated for children. The major toxicity related to isoniazid is hepatic toxicity. As many as 10% of children will experience elevated serum aminotransferase levels while taking this medication. These liver enzyme abnormalities are rarely severe, and most children can be followed with clinical signs and symptoms instead of routine biochemical monitoring. Patients with disseminated forms of tuberculosis along with postpubescent or pregnant adolescent women are more likely to have hepatic complications and do require routine transaminase monitoring every 1 to 2 months while on therapy. Isoniazid may interfere with the metabolism of phenytoin, which will lead to elevated levels. If isoniazid is used in doses exceeding 10 mg/kg/day in combination with rifampin, hepatotoxicity can occur. Children on such regimens, however, usually can be followed clinically.

Rifampin

Rifampin as a bactericidal for M tuberculosis, is relatively nontoxic and generally well tolerated at a dose of 15 mg/kg/day. Although approximately three quarters of this medication is protein bound, it penetrates well into most tissues with the exception of the meninges. Rifampin can penetrate the meninges only when inflammation is present. Currently, the commercially available forms of rifampin are in milligram doses that are inconvenient for many children. A suspension can be made from the capsules that may facilitate administration to smaller children. If the suspension is used, it should only be taken without food due to its erratic absorption. The most common side effect from rifampin is gastrointestinal upset. Other reactions include skin eruptions, hepatitis, and occasionally thrombocytopenia or cholestatic jaundice. Rifampin is excreted in urine, tears, sweat, and other body fluids. These body fluids will become

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orange and contact lenses will become discolored while consuming this medication. This discoloration of body fluids become a useful indicator of adherence to therapy. In addition, rifampin may alter the effectiveness of oral contraceptives.

Pyrazinamide

Clinicians may be most unfamiliar with pyrazinamide. This antituberculosis agent exerts its maximal effect during the early phase of therapy (2 months) rather than throughout the treatment course. It is absorbed very well from the gastrointestinal tract and will penetrate into most tissues, including cerebrospinal fluid. The optimal dose in children has never been established due to the lack of pharmacokinetic data. Doses of 30 mg/kg/day are effective in adults and are well tolerated by children. Liver dysfunction, gastrointestinal upset, and skin rashes can be seen with pyrazinamide administration. Adults may develop symptomatic hyperuricemia with arthralgias and arthritis, but these symptoms are extremely rare in children.

Streptomycin

Streptomycin is a bactericidal medication, but has been in relatively short supply in the United States recently. This medication is not well absorbed from the gastrointestinal tract and must be given intramuscularly at a usual dose of 20 mg/kg/day. Streptomycin has good tissue penetration, but will enter the cerebrospinal fluid only when there is inflammation. The most common serious side effect is ototoxicity. This usually results only in tinnitus and vertigo, but hearing loss may occur also. Ototoxicity is more likely to develop if other ototoxic medications are used in conjunction with streptomycin.

Ethambutol

Ethambutol is rarely used in the routine treatment of uncomplicated childhood tuberculosis. This medication is considered to be bacteriostatic at 15 mg/kg/day and bactericidal at 25 mg/kg/day. It is easily administered and well absorbed, but penetrates poorly into the cerebrospinal fluid, even in the presence of inflamed meninges. Ethambutol is used primarily
when there is a high likelihood of initial drug resistance. Retrobulbar neuritis is the most frequent and serious adverse effect of this medication. Symptoms will include blurred vision, central scotomata, and red-green color blindness. This complication appears to be dose related and is rarely seen when persons are given a daily dose of 15 mg/kg/day. The frequency of ocular side effects is increased in patients who have concomitant renal failure. In children who are too young to voice visual acuity changes, ethambutol should be used only if there is no possibility of an effective alternative medication.

Other Medications
Para-aminosalicylic acid, ethionamide, cycloserine, capreomycin, kanamycin, and thioacetazone are other medications that have been used occasionally for the treatment of tuberculosis in children. In recent years, there have been a number of new drugs evaluated in children and adults with activity against M tuberculosis. These include amikacin, rifabutin, clofazimine, and quinolones, macrolides, and beta-lactams. Although the recent increase in the occurrence of multidrug-resistant tuberculosis may create situations where the use of these newer medications may be considered, their use currently is discouraged prior to consultation with an expert in tuberculosis therapy.

TREATMENT
Drug-Susceptible Infection
Children who are infected with tuberculosis, but demonstrate no active disease, will manifest their infection with only a positive tuberculin skin test. This is referred to as an asymptomatic infection. The appropriate criteria for defining a positive skin test reaction depends on the population being tested. Such children should receive therapy so that reactivation of their disease later in life will not occur. It is currently recommended that such children should receive isoniazid for 9 months (Table 2).10

Pulmonary tuberculosis now can be treated with a 6-month regimen containing multiple drugs (Table 2). Isoniazid, rifampin, and pyrazinamide are taken daily for 2 months followed by isoniazid and rifampin daily or twice weekly (directly observed therapy) for 4 months.10 An alternative to this regimen is 9 months of daily isoniazid and rifampin. This regimen can be used only in areas where low resistance rates to isoniazid and rifampin are documented and susceptibility patterns are continually monitored. This regimen may be less desirable even in areas of low resistance, however, because of the additional 3 months of therapy.

Patients who elect to complete their course of treatment with twice-weekly dosing should be monitored very closely. Ideally, these patients should be given their medications only under directly observed therapy. Directly observed therapy means that a health-care provider or other responsible person watches the patient as they ingest their antituberculosis medications. The medications may be given in an office or clinic setting or they may be given in the patient's home. This route is less expensive than daily administered therapy and can eliminate the problem of secondary drug resistance. Consideration should be given to treating all patients with directly observed therapy.11

The optimal treatment for most forms of nonlife-threatening extrapulmonary tuberculosis is the same as for pulmonary disease. For the more complicated and disseminated forms of tuberculous disease (meningitis, miliary disease, and bone/joint infection), the American Academy of Pediatrics recommends 1 year of therapy (Table 2).10 Bacteriologic evaluation in these types of illnesses often is limited by the relative inaccessibility of the sites of disease. The treatment response of such patients, therefore, often is judged by the use of clinical and roentgenographic findings. Patients should be initially placed on isoniazid, rifampin, pyrazinamide, and streptomycin and treated daily for 2 months. After the initial 2 months, 10 months of daily isoniazid and rifampin are used. If adherence to therapy is a problem, directly observed therapy should be used for the entire duration. Shorter treatment regimens have been used successfully, but are not currently recommended in children.12-14

Drug-Resistant Infection
The incidence of multiple drug-resistant tuberculosis is on the rise in the United States. In a recent study in
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New York City, 33% of M tuberculosis isolates were resistant to one or more antituberculosis medications. Twenty-six percent of the patients demonstrated resistance to isoniazid and 19% were resistant to both isoniazid and rifampin. Issues concerning the possibility of drug resistance should be raised for children living in high-risk situations. Children at risk would be those who are living with adults who have immigrated from high-risk regions (i.e., Southeast Asia, the Caribbean, and certain areas of the United States), and adults who are homeless, infected with the human immunodeficiency virus (HIV), have a prior history of antituberculosis therapy, or have been in prison. If there is a high probability of isoniazid resistance, an asymptomatically infected child should receive 9 months of rifampin. When drug-resistant tuberculous disease is suspected, a four-drug regimen, including isoniazid, rifampin, pyrazinamide, and streptomycin should be started. Ethambutol may be substituted if streptomycin is unavailable or not tolerated. If susceptibility patterns demonstrate that the organism is not susceptible to at least two of the medications, a drug regimen should be constructed with the assistance of an expert in the field of childhood tuberculosis. Adult patients with multiple drug-resistant tuberculous infections have only a 50% response rate and have a higher mortality rate than patients infected with isolates susceptible to isoniazid and rifampin. In cases of isoniazid or rifampin resistance, short-course therapy should not be used, and treatment should be extended to 12 to 18 months.

HUMAN IMMUNODEFICIENCY VIRUS

The optimal therapy for children co-infected with tuberculosis and HIV has not been established. In adult patients with HIV and tuberculosis, conventional therapy is extended to 9 months or to 6 months after sputum cultures become sterile, whichever is longer. The extension of therapy may not be as important as the adherence to the treatment plan. Because data are lacking in children co-infected with HIV and tuberculosis, most clinicians are treating children in a manner similar to adults. Children with drug-susceptible tuberculosis and HIV infection have been treated successfully with 2 months of isoniazid, rifampin, and pyrazinamide, followed by daily isoniazid and rifampin to complete 12 months of therapy. Children infected with HIV and multiple drug-resistant tuberculosis have a very high mortality rate despite aggressive therapy in the small number of cases reported to date. Because of the potential severity of disease in HIV-infected patients, the use of directly observed therapy is recommended even more strongly in this group. Care should be taken with patients co-infected with HIV who are receiving antifungal agents (i.e., ketoconazole and fluconazole) since these medications may interfere with specific antituberculosis medications (i.e., isoniazid and rifampin).

CORTICOSTEROIDS

Corticosteroid therapy has been demonstrated to decrease mortality rates and long-term neurologic sequelae in patients with tuberculous meningitis. The beneficial effect is thought to occur by reducing vasculitis, inflammation, and intracranial pressure. Concern over the lack of penetration of antituberculosis medications into the cerebrospinal fluid due to the loss of meningeal inflammation with corticosteroid treatment has not been demonstrated. Children with enlarged hilar lymph nodes that compromise the airway, or those with pleural or pericardial effusion have been shown to benefit from corticosteroids. Corticosteroids have been used in cases of miliary disease to mitigate alveolocapillary block. Prednisone (1 to 2 mg/kg/day) for 4 to 6 weeks with a 2-to-3-week taper is used most often. There is no convincing evidence available that one corticosteroid preparation is superior to another in these cases. Corticosteroids should be used only in tuberculous therapy when accompanied by adequate antituberculous therapy.

FOLLOW-UP

Although tuberculosis is not difficult to treat, consultation with an expert in tuberculosis is encouraged in cases of drug-resistant tuberculosis, severe forms that require corticosteroid therapy, or in children co-infected with HIV. Centers that deal with childhood tuberculosis will have programs in place to overcome problems that develop during the course of therapy. The major problem with long-term drug therapy of any type is adherence to the treatment plan. The healthcare provider must take the time to explain how to take the medications and why it is so important to adhere to therapy. It is preferable to educate patients and their families in simple terms using their native language. Written instructions for patients who read or picture instructions for illiterate patients should be supplied. Children on therapy for tuberculosis should be monitored closely (i.e., every 4 to 6 weeks) during treatment to ensure adherence, to monitor for toxic effects of the medications, and to assess adequacy of therapy. Nonad-
herence in the form of missed appointments or missed medications should not be tolerated. Problem patients should be brought to the attention of the local public health department so it can assist in correcting these problems. Directly observed therapy should be encouraged in all cases and used in any case where there is a question of adherence.

The occurrence of significant adverse reactions to antituberculosis medications is rare in children. Monitoring for these adverse events by clinical examination is preferable over the use of routine laboratory analysis. Postpubescent or pregnant women are an exception; these patients, as well as those with the more severe forms of tuberculosis, have a higher incidence of hepatotoxicity and require routine laboratory evaluation during therapy.

Chest roentgenograms are very slow to return to normal in individuals with pulmonary tuberculosis. Abnormal chest roentgenograms with hilar adenopathy may continue for years. The first follow-up chest roentgenogram can be done 1 to 2 months into therapy for children with pulmonary tuberculosis to ensure there has been no progression of disease. Another roentgenogram usually is not required until the medications are stopped. If there has been significant improvement, the medications can be discontinued, but a normal chest roentgenogram is not a necessary criterion for stopping medications. Once medications have been stopped, the child can be seen at 3- to 6-month intervals to monitor the improvement of the chest roentgenogram.

REFERENCES