SPECIAL ARTICLE

CURRENT CONCEPTS OF EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT OF CHILDHOOD TUBERCULOSIS IN THE UNITED STATES

J.R. Starke

Despite the availability of effective anti-tuberculosis drugs, tuberculosis remains an important cause of morbidity, mortality and healthcare expenditures in the United States. It is estimated that one billion people worldwide are infected with the tubercle bacillus and that one to three million deaths occur annually from tuberculosis(1). In the United States, over 23,000 new cases occur every year and the incidence has been rising during the past five years. Approximately 1200 new cases occur annually in children in the United States. These increases are thought to be due to the prevalence of infection with the Human Immunodeficiency Virus (HIV), and influx of foreign-born individuals at high risk of tuberculosis.

Tuberculosis persists in the United States despite the fact that modern medical science has developed the tools to virtually eliminate the disease. Not only is this disease curable, but also it is preventable if established public health principles are adhered to. One of the major barriers to the successful control of tuberculosis in the United States is complacency among the general public and healthcare providers. Many medical schools no longer adequately teach the subject of tuberculosis. As a result, the diagnosis increasingly is being made when disease is advanced.

If the United States is to achieve its goal of eliminating tuberculosis, the program must focus great effort on children because they are the future reservoir for the disease. Tuberculosis cases in children are important public health markers for a community because they represent ongoing transmission of tuberculosis and, at least, a partial failure of current tuberculosis control efforts.

The city where I practice, Houston, Texas, consistently has had a high tuberculosis case rate in children. In the past several years, a number of United States cities have experienced significant increases in childhood tuberculosis, indicative of a general failure of our public health system to prevent transmittable diseases.

This review will focus on important aspects of epidemiology, diagnosis, treatment and prevention of tuberculosis among children. It will represent the current state of the art of practice in the United States and give some insight into future directions in each of these areas.

Epidemiology

The incidence of tuberculosis in the United States declined steadily for a twenty-five year period until 1985, when it leveled off. The current annual United
States case rate for all ages is 9.8 per 100,000 population(2). The number of cases in children annually is 5-6% of the total number of cases. In 1985, of the 1261 cases in children below 15 years of age, 789 cases, or 63%, occurred in children below 5 years of age(3). The interval between ages 5 and 14 years has long been known as “the favored age” for tuberculosis, since children in this age range have a consistently lower active case rate (not infection rate) than any other segment of the population.

The most recent year for which complete statistics are available in the United States is 1985(3). In that year, of the 1,261 patients with childhood tuberculosis, 344 (27.3%) were white-Hispanic, 456 (36.2%) were black, 254 (20.1%) were white-non Hispanic, 47 (3.7%) were native American, and 160 (12.7%) were Asian/Pacific Islander. Therefore, 80% of the cases occurred in minority groups. There were 221 (17.5%) cases in foreign-born children. Tuberculosis incidence rates for southeast Asian refugees were as much as 70 times higher than those for other persons living in the United States(4). The disease is geographically focal as only 12% of United States counties reported one or more tuberculosis cases in children under age 15. Thus, cases of childhood tuberculosis in the United States tend to cluster in certain racial and ethnic groups and in certain geographic locales.

There have been some important shifts in the epidemiology of tuberculosis in adults in the United States which profoundly affect children. Individuals in certain groups are at higher risk for tuberculosis than the general population (Table I). There really are two separate risk factors for the development of tuberculous disease: (i) risk of acquiring the infection, and (ii) risk of infection developing into disease. Risk factors for the former involve the environment of the patient while risk factors for the latter are related to the host’s ability to prevent development of disease. The likelihood of a child developing tuberculous infection or disease is directly related to the likelihood of adults in the child’s environment developing active disease. At The Children’s Tuberculosis Clinic in Houston, Texas, 80% of tuberculosis cases in children can be traced to an adult case in the household. Other environments such as prisons, nursing homes, shelters for the homeless and daycare centers may promote transmission. Children with tuberculosis rarely, if ever, infect other children(5). Therefore, for every child with tuberculous infection, there must be an adult in the environment with active contagious tuberculosis.

In many cities in the United States, there has been a distinct shift in age of onset of tuberculous disease. In the majority white non-Hispanic population, tuberculosis is a disease of older adults, those who were infected decades ago in childhood with the tubercle bacillus. However, in minority groups, especially among blacks and white Hispanics, tuberculosis is increasingly a disease of young adults during the child-bearing years. With this increase in incidence in young adults, one would predict a subsequent increase in childhood tuberculosis. This is already occurring in several major cities including Los Angeles and New York City, which have had explosions of tuberculosis in children within the past two years. The major reason for the increase in young adult cases in the United States probably is HIV infection but difficulties with public health systems and access to medical care also may be contributing factors.

There have been several recent studies
TABLE 1—High Risk Groups for TB in the United States

<table>
<thead>
<tr>
<th>Group</th>
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<tbody>
<tr>
<td>Children less than 5 years old</td>
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<tr>
<td>Foreign-born persons from high prevalence countries</td>
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<tr>
<td>Intravenous drug users</td>
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<tr>
<td>Medically underserved low income populations</td>
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<tr>
<td>Residents of long-term care facilities</td>
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<tr>
<td>Prisons</td>
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<tr>
<td>Nursing homes</td>
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<tr>
<td>Mental institutions</td>
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<tr>
<td>Persons infected with the HIV</td>
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<tr>
<td>Health care workers</td>
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In both adults and children in the United States determining what proportion of cases might have been prevented if truly optimal public health services had been available(6,7). Among adults, as many as 35% of cases might have been preventable with better screening and treatment programs, while among children in Houston, approximately one-third of cases would have been preventable if better public health resources had been available.

Diagnosis

The diagnosis of childhood tuberculosis can be extremely difficult since positive cultures are obtained much less frequently than they are in adults with active disease. In the majority of cases, the diagnosis is established by a combination of information including known exposure to an adult with active tuberculosis, a positive tuberculin skin test, a reasonable negative evaluation for other possible etiologies, a chest radiograph and/or physical examination consistent with tuberculous disease, and a response to antituberculosis chemotherapy.

Symptoms and Physical Signs

Considering the degree of radiographic change seen in many children with pulmonary tuberculosis, the symptoms and physical signs are surprisingly meager. At the Children's Tuberculosis Clinic in Houston, more than one half of the children with moderate to severe abnormalities on chest radiograph are asymptomatic at diagnosis, having been found through tracing of an adult case of active tuberculosis(8). Young children, especially infants less than one year of age, are more likely to have symptoms.

Occasionally, the initiation of the primary tuberculous infection is marked by low grade fever and mild cough, which resolve in several days. As hypersensitivity to tuberculous antigens increases and the pulmonary inflammation progresses, nonspecific symptoms such as fever, cough, weight loss and night sweats may occur. Young infants may demonstrate “a failure-to-thrive” pattern. However, there is no specific presentation typical for tuberculosis. Pulmonary signs and symptoms are usually absent. Some infants with bronchial obstruction will show signs of air trapping such as wheezing or decreased breath sounds, which may be accompanied by tachypnea or, rarely, frank respiratory distress. In some infants, the respiratory signs will diminish as the segment or lobe collapses. Occasionally, the nonspecific symptoms and pulmonary signs will be alleviated by antibiotics, suggesting that bacterial superinfection may play a role in pathogenesis.

As the tuberculosis case rate in the United States has decreased over the past few decades, the proportion of extrapulmonary cases has increased(9,10). In Houston, almost one third of the children with active tuberculosis have extrapulmonary manifestations. Whereas pulmonary disease frequently is clinically silent extra-
pulmonary tuberculosis is usually diagnosed after signs or symptoms have occurred. Other than pleural tuberculosis, the most common forms of extrapulmonary tuberculosis are adenitis, meningitis and disseminated disease. Infections of other sites occur but are rare in the United States.

Superficial lymph node infection with *Mycobacterium tuberculosis* usually occurs in the cervical or supraclavicular region. The affected nodes typically are nontender, firm and multiple. The overlying skin may develop erythema or a purple hue. Sinus tract formation is unusual. Although other conditions in the United States, such as cat scratch disease, may have a similar presentation, the greatest difficulty is distinguishing tuberculosis from nontuberculous mycobacterial infections(11,12). The incidence of nontuberculous mycobacterial adenitis is highest in children less than 4 years of age living in rural areas in the southeastern United States. Children with *M. tuberculosis* adenitis more commonly live in cities and have an exposure history for tuberculosis. The chest radiograph is more commonly abnormal in cases caused by *M. tuberculosis* but intrathoracic adenopathy may be present with either infection. It is important to distinguish lymph node disease due to nontuberculous mycobacteria from that caused by tuberculosis since excision will alleviate nontuberculous mycobacterial infection while tuberculous adenitis always requires chemotherapy. In Houston, Texas, approximately 90% of the mycobacterial infections of the neck are due to nontuberculous mycobacteria.

It is interesting to note that BCG vaccination has never achieved widespread use in the United States, and central nervous system tuberculosis continues to occur. I have cared for 22 children in the last five years with tuberculous meningitis, none of whom had prior BCG vaccination. Most of these children were younger than 2 years of age. Their initial signs were nonspecific including fever, personality changes, listlessness or irritability and loss of developmental milestones. Virtually all of these patients have had some degree of hydrocephalus at diagnosis. Other common signs or symptoms have included cranial nerve palsies, vomiting, lethargy and convulsions. Computerized tomography of the brain reveals the communicating hydrocephalus and brain stem meningitis. The tuberculin skin test is negative in up to 40% of cases of documented tuberculous meningitis(13,14). The most important aid in diagnosis is knowing a history of exposure to an adult with active tuberculosis.

**Chest Radiograph**

The radiographic findings in childhood tuberculosis in the United States reflect the pathophysiology of the infection. The primary infection begins with deposition of infected droplets in the lung alveoli. The parenchymal inflammation is usually not visible on chest radiograph but a localized nonspecific infiltrate may be seen. All lobar segments of the lung are at equal risk of being seeded. Usually only one site of infection is present but in 25% of cases, multiple lung foci occur. Spread of infection to regional lymph nodes occurs early. The hallmark of initial tuberculous infection is the relatively large size and importance of the hilar adenitis compared with the relatively insignificant size of the initial parenchymal focus(15-17).

In most cases, the mild parenchymal infiltrate and adenitis resolve spontaneously. The child is left with a positive reaction to a tuberculin skin test and this
Child is said to have tuberculous infection without disease and is a candidate for what we call preventive therapy. In some children, especially young infants, the lymph nodes continue to enlarge. Bronchial obstruction begins as the nodes impinge on the neighboring regional bronchus compressing it and causing diffuse inflammation of its wall(18). As destruction continues, perforation of the bronchus and formation of thick caseum in the lumen also may occlude the bronchus. The common sequence is hilar adenopathy followed by localized hyperaeration and, eventually, atelectasis. The resulting radiographic shadows have been called "collapse consolidation", "segmental lesions" or "epituberculosis"(17,19). These findings are similar to those caused by foreign body aspiration but are quite different from those usually seen with bacterial or viral pneumonia. Segmental lesions are more common in infants than older children and tend to occur within months of the initial infection. Approximately 45% of children below a year of age who acquire tuberculous infection will develop a segmental lesion compared with only approximately 16% of children who acquire their infection at ages 11-15 years(20). With proper treatment, complete radiographic resolution of most segmental lesions occurs, although an occasional child will develop scarring and bronchiectasis. These destructive changes are most common if the primary infection is in the lower lobes. Rarely, liquefaction of the lung parenchyma occurs, leading to formation of a thin-walled, primary tuberculous cavity.

Other chest radiographic findings may occur with childhood tuberculosis in the United States. Localized pleural effusion frequently accompanies the primary pulmonary focus. Significant pleural effusion is rare in children less than 2 years of age and is almost never associated with the segmental lesion. Calcification, when it appears, results from caseation of the primary complex, especially the lymph nodes. It usually requires 6 months or more after inoculation to occur. Extensive calcification is uncommon when treatment is instituted early. Adult type reactivation tuberculosis, with typical thick-walled apical cavities, while rare in children, is more common in adolescence. Regional adenitis is not a feature of this presentation.

**Laboratory Tests and Cultures**

Routine laboratory tests, such as the complete blood count and white cell differential, rarely aid in the diagnosis of tuberculosis in the United States. Abnormalities of liver function may help suggest disseminated tuberculosis. White or red cells in urine sediment may indicate renal tuberculosis if other causes are ruled out. Analyses of infected body fluids—pleural, joint and cerebrospinal—showing lymphocytes, elevated protein, and decreased glucose suggest tuberculosis.

The most important laboratory test for the diagnosis and management of tuberculosis is a mycobacterial culture. In adults, isolation of the organism confirms the diagnosis and susceptibility testing directs therapy. In children, isolation of *Mycobacterium tuberculosis* is not necessary in many cases of pulmonary tuberculosis if the epidemiologic, skin test, and radiographic information is compatible with the disease. If the adult source case culture and susceptibility results are known, cultures from the child add little to management of the disease. However, when no source case is available, as when the child contracts tuberculosis in another country, the increasing incidence of drug resistant isolates of
M. tuberculosis dictates then attempts to culture the organism from the child should be made. Also, cultures are obtained from any patient suspected of having extrapulmonary tuberculosis, to confirm the diagnosis.

Sputum produced by an older child or adolescent with pulmonary tuberculosis may yield M. tuberculosis. Younger children rarely produce sputum. Gastric aspirates yield the organism in 30-40% of cases of pulmonary tuberculosis (8,21). For infants with extensive disease, in our clinic, the yield is greater than 80%. Gastric aspirates are more likely to yield the organism than are bronchial washings if they are obtained correctly. Aspiration should be done early in the morning as the child awakens, before the stomach empties itself of the overnight accumulation of secretions swallowed from the respiratory tract. The sample should be collected in saline-free fluid and the pH should be neutralized if processing will be delayed for more than several hours.

The traditional methods using Lowenstein-Jensen and Middlebrook's media require 4-6 weeks for isolation of the organism and another 3-4 weeks for susceptibility testing. The BACTEC radiometric system uses fatty acid substrates labeled with 14C. As the mycobacteria metabolize these fatty acids, 14CO2 is released and can be measured as a marker of bacterial growth. Nontuberculous mycobacteria can be distinguished from M. tuberculosis by employing a second substrate. The BACTEC system, now used in most mycobacteriology reference laboratories in the United States, yields culture and susceptibility results in as little as 7-10 days and is more sensitive for sputum cultures than traditional media (22,23). Little information about BACTEC methodology for gastric aspirates or extrapulmonary cultures is available. Whether BACTEC or traditional isolation procedures are used, the laboratory should be alerted if a drug resistant isolate is suspected, since its isolation may take longer and be more difficult.

The Tuberculin Skin Test

Primary tuberculosis refers to infection in a person with no prior immunity to the disease. In most cases, primary infection is silent, although clinically evident disease is seen much more commonly in children than in adults. A positive tuberculin skin test is the hallmark of the primary infection. Few tests in medical practice in the United States are as widely used yet as misunderstood as the tuberculin skin test. One must be familiar with its limitations and variations to use it effectively. In the United States, BCG has never been given as a routine vaccination. Therefore, the problem of cross-reaction with BCG is much less widespread than it is in other parts of the world. The elimination of the "BCG variable" in interpreting tuberculin skin tests has made it a very useful tool for diagnosis and tuberculosis control in the United States.

There are two major techniques currently used for tuberculin skin testing. The most accurate standardized test is the Mantoux—the intradermal injection of 5 tuberculin units (TU) of purified protein derivative (PPD) in 0.1 ml of diluent also containing the stabilizing agent, polysorbate 80. This technique should always be used in patients suspected of having tuberculosis and in contact or associate investigations. The test is read as the transverse diameter of induration present at 48-72 hours. In the United States, for purposes of screening asymptomatic, low incidence
populations, multiple puncture tests have enjoyed widespread use. However, these tests are qualitative only, yielding negative, positive or questionable results. In general, there is little significant difference among the different available products with false positive results ranging from 5-10% and false negative results ranging from 2-8% (24,25). The multipuncture tests should never be used in groups at high risk for tuberculosis. Since most screening in the United States is now directed at high risk groups, the multipuncture skin tests have all but become obsolete.

The Mantoux test is subject to a variety of influences relating to both the testing procedure and the host. Testing technique must be precise and consistent. Reactions can be difficult to interpret. Although experienced healthcare providers may demonstrate good inter-observer agreement, inexperienced observers, including parents, frequently report inaccurate results.

A variety of host related factors such as nutrition, immunosuppression, age, viral infections or immunizations with live viral vaccines and presence of disseminated tuberculosis can alter the tuberculin reactivity of the patient (26,27). Approximately 10% of adults and children with culture documented tuberculosis do not react initially to PPD (8,28,29). Corticosteroid therapy may depress the reaction to tuberculin but the effect is variable and may be limited to several months. A host of factors related to test technique may lead to false negative tuberculin reactions (26).

On the other hand, a problem which is especially prevalent in the United States is recent exposure to environmental nontuberculous mycobacteria. This can result in cross sensitization and a false positive reaction to the Mantoux skin test (28). Immunization with BCG also may lead to a subsequent positive skin test (29). Usually the nontuberculous mycobacteria and BCG cross reactions are transient and produce less than 12 mm of induration.

The key question related to the Mantoux tuberculin testing is what amount of induration should be considered significant, a true indication of tuberculous infection. This "cutpoint" varies with the population being studied and is dependent upon epidemiologic factors. For instance, in areas of the United States where nontuberculous mycobacteria are common, only 5% of children in whom a Mantoux tuberculin test yields 5-9 mm of induration truly are infected with M. tuberculosis. However, if a child has the same reaction, but is a contact to a known case of tuberculosis, the probability that the child is infected with M. tuberculosis is almost 50% (26). The critical information is epidemiologic--has exposure occurred? Again the importance of history and exposure tracing is obvious.

The definitions of a positive and negative tuberculin skin test have recently changed in the United States based on new Centers for Disease Control and the American Thoracic Society criteria. The basic principle is that the likelihood of a test being significant is directly related to the risk of the patient having been exposed to tuberculosis. A 5 mm reaction is considered significant in persons suspected of having clinical tuberculosis, in contacts of known cases of tuberculosis and in the immunocompromised, especially patients with HIV infection. A reaction of 10 mm is considered significant for persons at high risk of acquiring tuberculosis, specifically foreign-born individuals from countries with high rates of tuberculosis, people who have spent time in prisons, nursing homes or other institutions, intravenous drug
abusers, the homeless, persons who live in neighborhoods with higher than average rates of tuberculosis, and healthcare workers. For other individuals considered to be at low risk of tuberculosis, a 15 mm skin test reaction is considered significant. In a large group of individuals with active tuberculosis, the median skin test reaction ranges between 12 and 18 mm. The cut-points determined above are designed to minimize false negative tests, particularly in children.

**New Diagnostic Techniques**

Until recently there have been few advances in diagnostic techniques for tuberculosis. The modern revolution of immunochemistry and genetic engineering is finally being applied to mycobacterial diseases. Although the techniques described in this section are not widely available, their development is imminent.

The serodiagnosis of tuberculosis has been envisioned since 1898 when Arloing developed the first agglutination test. Two methodologic problems have slowed progress—a lack of description and isolation of specific mycobacterial antigens, and a poor understanding of the humeral response to mycobacterial infection. Serologic diagnosis has been attempted using a variety of complex antigens including PPD, BCG, mycobacterial antigens 5 and 6, other complex polysaccharide and protein antigens(30,34). Enzyme linked immunosorbent assay (ELISA) has been the technique used most commonly in field trials of tuberculosis serology. The major problem with most serologic tests has been their specificity, that is, there are too many false positive tests to make the technique useful on a massive scale(30). Many systems have had sensitivities and specificities equivalent to a sputum smear which has rendered them not particularly useful for diagnosis of pulmonary tuberculosis in adults. However, a similar sensitivity and specificity would represent a tremendous advance for the diagnosis of pulmonary disease in children or extrapulmonary tuberculosis, especially tuberculous meningitis. A small study in Argentina of children with pulmonary tuberculosis using the antigen 5 ELISA yielded a sensitivity of 86% and a specificity of 100%(35). In children with tuberculous meningitis, ELISA using antigen 5 detected immunoglobulin G (IgG) antibody in the CSF in fewer than 20% of cases(36). However, other systems have had much higher success rates in the diagnosis of tuberculous meningitis. In the United States, no assay has achieved significant specificity and sensitivity to be in widespread or commercial use. As in India and other countries, many specific laboratories and medical centers have their own tests with extremely variable results.

Other new diagnostic advances depend not on the host response to tuberculosis but on direct detection of components of products of the mycobacterium. The first such technique to be in widespread use involved DNA probes, which are complementary to specific ribosomal RNA or DNA sequences of either the mycobacterial genus or a particular mycobacterial species, such as *M. tuberculosis*(37). Radiolabeled DNA is added to a preparation containing the mycobacterial RNA or DNA. After hybridization occurs, unlabeled RNA and DNA are washed away and the amount of hybridization is measured in a gamma counter. Indirect probes, those used on colonies or mycobacteria isolated on solid media from body fluids or tissue, already are commercially available with sensitivities and specificities approaching.
100%. Direct probes, those used directly on samples from patients, currently are under development but have not achieved a sensitivity or specificity adequate for widespread use in patients.

A very promising advance in DNA technology has been the adaptation of the polymerase chain reaction (PCR) to mycobacterial populations(38,39). This technique uses an enzyme to geometrically amplify DNA replication. Combined with a DNA probe, this technique may allow for identification of presence of mycobacteria in a 4 hour period of time. In pilot studies, this technique has been able to detect femtimole quantities of mycobacterial DNA(40,41). Many probes specific for M. tuberculosis are being developed in different laboratories. At present, no commercially available probe exists but it is likely such products will be available within the next several years. This technique will be especially useful for directly measuring the presence of mycobacterial DNA in patient samples and may be particularly exciting technology for diagnosis of childhood tuberculosis and extrapulmonary tuberculosis in adults and children.

Other investigations have attempted to detect structural components of mycobacteria directly. The most common group of substances studied has been mycolic acids, especially tuberculostearic acid. Again, femtimole quantities of mycolic acids can be detected by use of high pressure liquid chromatography and gas chromatography(42,43). The technique has been applied directly to sputum, serum and cerebrospinal fluid(44,45). In many investigations, the sensitivity has been greater than 95%, but the test requires use of complex techniques which are not available in most laboratories throughout the world. Another advantage of this technique is that each species of mycobacteria has its own “fingerprint” of mycolic acids allowing for very rapid speciation of a mycobacterium isolated from a patient sample. This technique is being used routinely in some reference laboratories in the United States.

Treatment

The treatment of tuberculosis has undergone major changes within the past 10 years. As recently as the early 1980s, recommended treatment durations for adults and children were as long as 18 months. Although those regimens are effective if properly used, the actual failure rates are higher because of poor compliance among patients which leads to both relapse and emergence of drug resistance. The new regimens are often called “short course” chemotherapy because treatment durations as short as six months are routinely successful. However, the key to the new approach is not the short duration but the intensive initial therapy with several bactericidal antituberculosis drugs.

Microbiologic Rationale for Treatment

Several microbiologic characteristics of Mycobacterium tuberculosis have led to an hypothesis concerning the action of various drugs and drug combinations(46-52). The tubercle bacillus can be killed only during replication which is most frequent among organisms that are metabolically active(50). The bacilli in a host exist as three different bacterial populations. Organisms in each population have different rates of metabolic activity and replication. Mycobacterium tuberculosis is an obligate aerobe and activity rates vary with oxygen supply. Bacilli are active and replicate freely where oxygen tension is high. A neutral or alka-
line pH also promotes metabolic activity and growth. Environmental conditions for growth are best in cavities, leading to a very large bacterial population.(51) Adults with reactivation type pulmonary tuberculosis usually have all three populations of tubercle bacilli. Children with primary pulmonary tuberculosis and patients with only extrapulmonary tuberculosis usually are infected with a much smaller number of tubercle bacilli, because the cavitary population is not present.

Another important bacteriologic consideration for the treatment of tuberculosis is the presence of naturally occurring drug resistant mutants in large bacterial populations, even before chemotherapy is begun.(52) Although a population of bacilli as a whole may be considered "drug-susceptible" a subpopulation of drug resistant mutants occurs at a fairly predictable frequency. The mean frequency of these drug-resistant mutants is about 10^-6 but varies among drugs; streptomycin, 10^-5; isoniazid, 10^-6; and rifampin, 10^-7. Therefore, a cavity containing 10^9 tubercle bacilli has hundreds to thousands of drug resistance mutants whereas a closed caseous lesion with only 10^6 tubercle bacilli has few if any resistant mutants.

The combination of bacterial population size and drug resistant mutations explains why single antimicrobial drugs cannot cure cavitary tuberculosis. In the mid-1940s, streptomycin was administered alone to adults with cavitary pulmonary tuberculosis. In three months, 80% of patients had significant numbers of streptomycin resistant organisms.(53) This phenomenon has been observed for every antituberculosis drug developed subsequently. However, the natural occurrence of resistance to one drug is independent of resistance to any other drug. Therefore, the chance that a mutant is naturally resistant to two drugs is on the order of 10^-11 to 10^-13. Populations of this size do not occur in patients and mutants naturally resistant to two drugs are essentially nonexistent.

In general, the major biologic determinant of antituberculosis therapy is the size of the bacillary population in the patient. For patients with large bacterial populations, many drug resistant mutants are present and at least two antituberculosis drugs must be used. Conversely, for patients with infection but no disease, the bacterial population is very small (about 10^3 to 10^5 organisms); drug resistant mutants are rare and a single drug such as isoniazid can be used. Children with primary pulmonary tuberculosis and patients with extrapulmonary tuberculosis have medium size populations where significant numbers of drug-resistant mutants may or may not be present. In general, these patients are treated with at least two bactericidal drugs.

Actions of Antituberculosis Drugs

Antituberculosis drugs may have several different activities. Bactericidal action refers to the ability of the drug to kill *M. tuberculosis*. This activity can be demonstrated in the test tube, in animal models or in an infected macrophage system(54,55). The sterilizing activity is the ability to kill all the bacilli in tuberculous lesions as rapidly as possible. The speed of killing becomes progressively slower during chemotherapy so sterilizing activity really measures the speed with which the last few viable bacilli are killed.(51) In humans, this activity is measured by the proportion of sputum cultures from adults with pulmonary tuberculosis that are negative after two months of therapy and the proportion
of relapses that occur after chemotherapy is discontinued. In general, sterilizing activity indicates the suitability of an agent for use in intensive short course regimens. The final activity is prevention of resistance. This is a dependent on the ability of the agent to inhibit growth analogous to bacteriostatic activity.

The earliest treatment regimens for tuberculosis combined the action of a bactericidal drug, such as isoniazid, with a bacteriostatic drug, such as para-aminosalicylic acid, that would suppress the resistant mutants(56,57). A small number of drug susceptible organisms survived despite chemotherapy with these combinations and 18-24 months of treatment were necessary to permit host defenses to eliminate persistent organisms(52).

The availability of rifampin and pyrazinamide, the most potent sterilizing drugs, affected radical change in antituberculosis chemotherapy. Rifampin in combination with isoniazid and streptomycin led to cure of almost 100% of patients with pulmonary tuberculosis in a treatment period of only 9 months(58). Pyrazinamide was discovered to have very potent activity against organisms located in an acid environment, especially those inside macrophages. The exact bactericidal mechanism of pyrazinamide is not clear. It does not kill tubercle bacilli in the test tube and has variable action within in vitro infected macrophage systems, depending on laboratory conditions(59,60). Clinical studies indicate that it contributes to early sterilization and exerts its maximum effect during the initial phase of therapy rather than throughout the full course of treatment(61).

Special Considerations for Tuberculosis in Children

Historically, recommendations for treating children with tuberculosis have been extrapolated from studies of adults with pulmonary tuberculosis. However, childhood tuberculosis differs from adult tuberculosis in several ways that may greatly affect treatment. Children usually develop tuberculous disease as an immediate complication of the primary infection, typically involving closed caseous lesions with relatively small numbers of mycobacteria. The large cavitary population of bacilli is usually absent in children. Because development of secondary resistance is proportional to the size of the bacterial load, children are less likely than adults to develop resistance while receiving therapy, even if compliance is poor. However, secondary resistance certainly can occur in young children.

Children also have a higher propensity to develop most extrapulmonary forms of tuberculosis than adults, especially disseminated disease and meningitis(62). It is important that antituberculosis agents penetrate a variety of tissues including the meninges. Isoniazid, rifampin and pyrazinamide cross inflamed and uninfamed meninges adequately while streptomycin crosses only when inflammation is present(63,64).

The pharmacokinetics of antituberculosis drugs differ between children and adults. In general, children tolerate larger doses per kilogram of body weight and have fewer adverse reactions than adults(65,66). It is unclear whether the higher serum concentrations of antituberculosis agents achieved in children have any therapeutic advantage, because the lower doses used in adults lead to serum concentrations many times higher than the minimal inhibitory concentration for M. tuberculosis. The lower rate of toxicity in children means that fewer interruptions in
therapy are necessary. However, children with severe forms of tuberculosis, especially disseminated disease and meningitis, experience more significant hepatotoxic reactions than less severely ill children treated with the same dosages per kilogram of isoniazid and rifampin, especially if the isoniazid dosage exceeds 10 mg/kg (67, 68). Malnutrition also appears to be a risk factor for hepatotoxicity in children (69).

A further difference between children and adults concerns how the medications are given. Most commercially available dosage forms are designed for use by adults. Giving the medications to young children involves crushing pills or making suspensions that are not well studied or standardized. Some dosage forms may not permit adequate absorption of medications (70). Many children experience difficulty taking the several antituberculosis medications required especially at the beginning of therapy, causing delays and interruptions potentially severe enough to affect adequacy of treatment.

Finally, as for adults, compliance with taking medications remains the single biggest problem in treating children with tuberculosis, many of whom live in social environments not conducive to consistency or completeness of care. In the United States, noncompliance rates as high as 50% are common. The ability to administer twice-a-week antituberculosis medications by a healthcare worker has become a necessary part of treatment programs in the United States.

Intensive Short Course Therapy in Children

Clinical trials of antituberculosis drugs in children are difficult to perform because of several aspects of the disease: (i) establishing the diagnosis of tuberculous disease in a child can be imprecise because cultures are positive less than 50% of the time; (ii) definitions of treatment failure and relapse of tuberculosis in a child are usually on clinical grounds because they are rarely associated with a positive culture; (iii) the natural history of primary pulmonary tuberculosis in a child is usually improvement even without drug therapy; (iv) it is difficult to compare results of trials performed in developing countries with those from technically advanced nations; and (v) well-controlled trials of tuberculosis treatment in children are rare because of the fairly small numbers of patients seen at most centers able to conduct such studies.

In 1983, Abernathy et al. reported successful treatment of 50 children in Arkansas with tuberculosis using isoniazid (10-20 mg/kg) and rifampin (10-20 mg/kg) daily for one month, followed by isoniazid (20-40 mg/kg/dose) and rifampin (10-20 mg/kg/dose) twice-a-week for 8 months (71). Diagnosis was usually established on clinical grounds. It should be noted that drug resistant rates for M. tuberculosis are extremely low in Arkansas.

During the past decade, there have been several major studies of six-month multiple drug therapy for tuberculous disease in children reported from a number of countries in both abstracts and articles (72-80) (Table II). These trials have used several different regimens with quite similar results. On the average, children were followed for about 2 years after treatment was completed. Regimens not using streptomycin were as successful as those that included it. Giving supervised twice-weekly medications during the continuation phase was as effective and safe as daily self administration. The overall success rate was
TABLE II—Published Results of 6-Month Treatment Regimens for TB in Children

<table>
<thead>
<tr>
<th>Year</th>
<th>Reference</th>
<th>Number of subjects</th>
<th>Regimens used</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>1980</td>
<td>(72)</td>
<td>54</td>
<td>2IRZS/4I₂Z₂S₂</td>
<td>1 failure (drug resistant)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2IRZ/4I₂Z₂</td>
<td>0 relapses</td>
</tr>
<tr>
<td>1984</td>
<td>(73)</td>
<td>241</td>
<td>2IRSZ/4IR</td>
<td>1% died (serious extrapulmonary disease)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 relapses</td>
</tr>
<tr>
<td>1985</td>
<td>(79)</td>
<td>223</td>
<td>2IRZ/10IR</td>
<td>0 failures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2IRZ/7IR</td>
<td>0 relapses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2IRZ/4IR</td>
<td>0 relapses</td>
</tr>
<tr>
<td>1985</td>
<td>(75)</td>
<td>185</td>
<td>2IRE/4IR</td>
<td>0 failures; 10% with abnormal CXR’s</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2IZE/41E</td>
<td>at end of 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6I₃R₂E₃</td>
<td>0 relapses</td>
</tr>
<tr>
<td>1989</td>
<td>(76)</td>
<td>40</td>
<td>2IRZ/4IR</td>
<td>0 failures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2IRZ/4₁₂R₂</td>
<td>0 relapses</td>
</tr>
<tr>
<td>1989</td>
<td>(77)</td>
<td>40</td>
<td>6IR</td>
<td>0 failures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6IRE</td>
<td>0 relapses</td>
</tr>
<tr>
<td>1990</td>
<td>(78)</td>
<td>118</td>
<td>2IRZ/4IR</td>
<td>“Significant” X-ray improvement in 90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2IRZ/4₁₂R₂</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>(79)</td>
<td>639</td>
<td>2IRZS/4₁₂R₂</td>
<td>12 died (serious extrapulmonary disease)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 relapses (mostly poorly compliant patients)</td>
</tr>
<tr>
<td>1990</td>
<td>(80)</td>
<td>76</td>
<td>2I₁₂R₂Z₂/4₁₂R₂</td>
<td>2 deaths, unrelated to TB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2IRZ/4₁₂R₂</td>
<td>0 relapses</td>
</tr>
</tbody>
</table>

* Treatment regimen codes show duration of initial phase of therapy, drugs used/duration of continuation phase, drugs used, rhythm of administration. I, isoniazid; R, rifampin, Z, pyrazinamide; S, streptomycin; E, ethambutol. For example, 2IR/4₁₂R₂ means 2 months of daily treatment with isoniazid and rifampin, followed by 4 months of twice-weekly treatment with isoniazid and rifampin. CXR’s—Chest X-rays.

Greater than 95% and the incidence of clinically significant adverse reactions was less than 2%. Two studies from India had a significant number of children with moderate to severe malnutrition(74,78). Approximately 10% of the patients in these two studies had improving but still abnormal chest radiographs after six months of therapy; the investigators chose to continue medications for several months more. In contrast, several studies have had children with abnormal chest radiographs at the end of therapy which continued to improve off therapy when medications were discontinued after six months of treatment. Several of the studies included extrapulmonary forms of tuberculosis which generally responded as well as intrathoracic disease.
One of the best controlled studies was from India, which compared a completely twice-a-week six month regimen with one using daily therapy for two months followed by twice-weekly therapy for four months(80). All drug administration was supervised for both regimens. Pulmonary, lymph node and disseminated tuberculosis responded well to each regimen. There were two deaths not associated with tuberculosis and no relapses during two years of post treatment follow-up. There was no significant clinical or biochemical hepatotoxicity. Unfortunately, 13% of patients absconded because the rapid clinical improvement was misinterpreted by the parents as cure of disease.

In all, more than 1,000 children with tuberculous disease treated with six month chemotherapy regimens have been reported. The success rates are high. The rates of adverse reactions are low and the number of relapses is extremely low. The most popular regimen has been two months of daily isoniazid, rifampin and pyrazinamide followed by four months of daily or twice-a-week rifampin and isoniazid. This regimen gives cure rates of approximately 98% or better.

Controlled trials of treatment of various forms of extrapulmonary tuberculosis are virtually nonexistent. In most reports, extrapulmonary forms have been combined with pulmonary cases and often are not analyzed separately. There have been several recent reviews of treatment of extrapulmonary tuberculosis in adults(81-83). Most non-lifethreatening forms of extrapulmonary tuberculosis respond well to a 9-month course of isoniazid and rifampin or six-month regimens using 3 or 4 drugs in the initial phase of therapy. One exception may be bone and joint tuberculosis which has been associated with a higher failure rate when short course chemotherapy is used.

Tuberculous meningitis usually is not included in trials of extrapulmonary tuberculosis therapy because of its serious nature and fairly low incidence. Treatment with isoniazid and rifampin for 12 months is generally effective(84). However, several studies have also reported effective treatment regimens of 6-12 months. A recent study in Thailand(85), compared 3 regimens for tuberculous meningitis in 325 children: (i) 12 months of daily isoniazid, streptomycin and ethambutol; (ii) 9 months of daily isoniazid, streptomycin and rifampin, and (iii) 6 months of daily isoniazid, streptomycin, rifampin and pyrazinamide. For mildly ill patients, the three regimens were equivalent. However, for patients with initial severe impairment of consciousness, there were significantly fewer deaths with the 6-month regimen that used pyrazinamide. Intensive initial therapy may be important to minimize neurologic sequelae.

**Drug Resistant Tuberculosis in Children**

The incidence of drug resistant tuberculosis is increasing in the United States and the world owing to poor compliance by the patient, the availability of antituberculosis drugs in noncontrolled over-the-counter formulations, and poor management by physicians. Drug resistance rates up to 80% have been noted in adults in some countries(86). Resistance is most common to streptomycin and isoniazid and is still rare for rifampin. Patterns of drug resistance in children in the United States tend to mirror those found in adult patients in the same population(87).

Therapy of drug resistant tuberculosis is successful only when at least 2 bacteri-
cidal drugs to which the infecting strain of M. tuberculosis is susceptible are given. If only one effective drug is given, secondary resistance to it will develop. When drug resistance is suspected, at least 3 and often 4 or 5 drugs should be given initially until the exact susceptibility pattern is determined and a more specific regimen can be designed. Duration of therapy is usually extended to at least 9-12 months if either isoniazid or rifampin can be used and 18 months if neither is available.

Prevention

There are several major methods of preventing tuberculosis (Table III). Primary methods prevent the initial tuberculosis infection and subsequent immunologic events, while secondary methods prevent an established infection from progressing to disease. The best methods of prevention for each population depend upon the effectiveness of each method, incidence and prevalence of tuberculous infection in the population, relative risk of progression to disease in infected individuals, age of the population, adverse reactions to each method, compliance by the patient and mobility of the population, and cost or resources available.

The United States and the Netherlands are the only two countries in the world that have not routinely used BCG vaccination as a method of tuberculosis control. In the United States, the emphasis has been on case management and contact investigation, coupled with isoniazid preventive therapy for infected individuals who have not yet developed active disease. The key to interruption of transmission of tuberculosis is rapid diagnosis and initiation of antituberculosis chemotherapy in diseased individuals. In the United States, the most efficient method of finding individuals with tuberculous infection and disease is via contact investigation of an adult source case. Usually the household of the source case is the highest risk setting. Individuals who are found to have positive tuberculin skin tests but no clinical or radiographic abnormalities are placed on isoniazid preventive therapy.

The treatment of individuals with asymptomatic tuberculous infection in order to prevent development of potentially communicable disease is an established practice in the United States. In the 1950s, investigators noted that children with primary tuberculosis treated with isoniazid did not develop previously common complications of the infection. A study of 2,750 with asymptomatic primary tuberculosis showed that preventive therapy with isoniazid produced a 94% reduction in tuberculous complications during a year of treatment and a 70% reduction over the subsequent 9 year period(88). Placebo controlled trials of isoniazid preventive therapy involving more than 125,000 subjects have been reported demonstrating a median reduction in tuberculosis of 60% in the treated group during the period of observation(89). When analysis is limited to subjects with good compliance, effectiveness approximates 90%. In children, the effectiveness has approached 100% and the effect has lasted for at least 30 years(90).

TABLE III—Methods of Preventing Tuberculosis

<table>
<thead>
<tr>
<th>Primary prevention</th>
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</thead>
<tbody>
<tr>
<td>Interrupting transmission</td>
</tr>
<tr>
<td>Case management, contact investigation</td>
</tr>
<tr>
<td>Environmental control—UV lights, airflow</td>
</tr>
<tr>
<td>Vaccination</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>
The most studied regimen for preventive therapy has been 5-10 mg of isoniazid per kilogram of body weight not exceeding 300 mg per day in a single daily oral dose for 12 months. Treatment lasting for more than 1 year did not confer additional protection. The role of isoniazid preventive therapy in countries where BCG has been in widespread use is controversial. BCG does not usually cause skin test induration of greater than 15 mm, although it can, on occasion. Skin test reactions between 10 and 15 mm can be due either to BCG or to tuberculous infection. However, if a child who has previously received BCG is in an environment where transmission of tuberculosis is likely, especially if the child has been in direct contact with an adult with proven pulmonary tuberculosis, any positive skin test in that child should be interpreted as possibly indicative of tuberculous infection, and use of isoniazid preventive therapy should be strongly considered. BCG vaccination does not prevent tuberculous infection(91). It undoubtedly lowers the incidence of severe forms of tuberculosis in children, especially disseminated and meningeval tuberculosis. However, the protective effect, especially for pulmonary tuberculosis in children, is far from 100% and isoniazid preventive therapy could be an effective adjunct to BCG vaccination in selective populations of children where BCG is used.

A current controversy in the United States concerns the optimal duration of isoniazid preventive therapy. To address this question, a large trial was conducted in Eastern Europe by the International Union Against Tuberculosis(92). Regimens of daily isoniazid taken for 12, 24 and 52 weeks were compared with a placebo for their ability to prevent tuberculous disease in adults with radiographically demonstrable fibrotic lesions. After five years of observation, treatment for 24 weeks prevented 65% of active cases compared with the placebo, while 52 week treatment prevented 75%. However, if analysis was restricted to patients who took at least 80% of the prescribed regimen, effectiveness changed to 69% for 24 weeks treatment versus 93% for 52 weeks treatment. Clearly, therapy for one year was more effective if patients were compliant but 24 week preventive therapy afforded a fairly high level of protection. The effectiveness of 12 weeks of preventive therapy was far below that of the other two regimens. A subsequent analysis of the study data concluded that the 24 week duration was more cost-effective than the 52 week regimen due mostly to smaller cost of supervision and drug toxicity(93). In the United States, 6-month preventive therapy has become standard practice for adults; however, most children are still treated with regimens of 9-12 months for preventive therapy.

Isoniazid is usually well tolerated especially in children. Isoniazid-related hepatitis is extremely rare; transient liver enzyme elevations may occur which almost always abate while on therapy. Isoniazid preventive therapy can be an important adjunct in the prevention of tuberculosis in any country of the world whether BCG has been given or not.

REFERENCES


NOTES AND NEWS

PEDiatric and NeONATAL EMERGENCIES
Publication of Indian Pediatrics

The book provides clear guidelines for the diagnosis and management of various problems that constitute emergencies. Prompt recognition of emergencies along with their appropriate and adequate initial management is essential to save lives and prevent complications. In a number of situations, the doctors cannot do very much and must send the patient to the casualty services of a hospital. One needs to be aware of such conditions. What not to do is also important. Emergencies in the newborn present very different and often unique problems that require special skills and proficiency for their recognition and management. A group of outstanding contributors have presented the various topics in an informative and lucid manner. The book has 58 chapters spread over 500 pages.

Pediatricians and physicians having first contact with emergencies in children as well as those responsible for the subsequent critical and intensive care will find this publication useful. It will be of particular interest for Postgraduate students.

The book can be procured from ‘Indian Pediatrics’ at a price of Rs. 150/- for soft cover or Rs. 175/- for hard cover. This price includes postal charges. The entire benefits from the sale of this book will go to the “Indian Pediatrics”. Demand drafts only, should be drawn in favour of Indian Pediatrics and mailed to the Editor.