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Tuberculosis in Infants and Children

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ABSTRACT One million children develop tuberculosis disease each year, and 210,000 die from complications of tuberculosis. Childhood tuberculosis is very different from adult tuberculosis in epidemiology, clinical and radiographic presentation, and treatment. This review highlights the many unique features of childhood tuberculosis, with special emphasis on very young children and adolescents, who are most likely to develop disease after infection has occurred.

The clinical expression of disease caused by *Mycobacterium tuberculosis* is greatly different in infants, children, and adolescents from what it is in adults (1, 2). Much adult pulmonary tuberculosis is caused by a reactivation of organisms which were lodged in the apices of the lungs during hematogenous dissemination at the time of infection. Childhood tuberculosis is usually a complication of the pathophysiologic events surrounding the initial infection. The interval between infection and disease is often long (years to decades) in adults but is often only weeks to months in small children. Children are more prone to developing extrapulmonary tuberculosis but rarely develop contagious pulmonary disease. As a result of the basic differences in pathophysiology of tuberculosis between adults and children, the approach to diagnosis, treatment, and prevention of infection and disease in children is necessarily different (3).

Many aspects of the various forms of childhood tuberculosis are discussed briefly in other chapters of this book. This chapter focuses on the fundamental nature of exposure, infection, and disease in children, emphasizing how and why children are approached differently from adults. The effects of these differences on the public health approach to tuberculosis control in children are also explained.

TERMINOLOGY

The terminology used to describe various stages and presentations of childhood tuberculosis often has been a source of confusion. It follows the pathophysiology, but the stages are sometimes not completely distinct in children.

Exposure means that the child has had significant contact—"shared the air"—with an adult or adolescent with potentially contagious pulmonary tuberculosis. The contact investigation—examining those individuals close to a suspected case of tuberculosis—is the most important activity in a community to prevent cases of tuberculosis in children (4, 5). The most frequent setting for exposure of a child is the household, but it can occur in a school, day care center, or other closed setting. In this stage, the initial test of infection (either a tuberculin skin test [TST] or interferon gamma [IFN-γ] release assay [IGRA]) is negative, the chest radiograph is normal, and the child lacks signs or symptoms of disease. Some exposed children may have inhaled droplet nuclei infected with *M. tuberculosis* and have early infection, but the clinician cannot know it because it takes up to 3 months for a test of infection to become positive. The World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC) recommend that children younger than 5 years of age and

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those infected with human immunodeficiency virus (HIV) in the exposure stage be treated to prevent the rapid development of disseminated or meningeal tuberculosis, which can occur before the tests of infection become reactive.

Infection occurs when the individual inhales droplet nuclei containing *M. tuberculosis*, which becomes established intracellularly within the lung and associated lymphoid tissue. The hallmark of tuberculosis infection is a reactive TST or IGRA. In this stage, the child has no signs or symptoms and the chest radiograph either is normal or reveals only granuloma or calcifications in the lung parenchyma and/or regional lymph nodes. In developed countries, virtually all children with tuberculosis infection should receive treatment, usually with isoniazid (INH), rifampin (RIF), or combination therapy with INH and a rifamycin, to prevent the development of disease in the near or distant future.

Disease occurs when signs and symptoms or radiographic manifestations caused by *M. tuberculosis* become apparent. Not all infected individuals have the same risk of developing disease. An immunocompetent adult with untreated tuberculosis infection has approximately a 5 to 10% lifetime risk of developing disease; one-half of the risk occurs in the first 2 to 3 years after infection. Historical studies have shown that up to 50% of immunocompetent infants with untreated tuberculosis infection develop disease, often serious, life-threatening forms, usually within 6 to 9 months.

The phrase primary tuberculosis has been used to describe childhood pulmonary disease that arises as a complication of the initial infection. Unfortunately, this phrase also has been used to describe the initial infection even in the absence of radiographic or clinical manifestations. Infection and the onset of disease are usually separated by time in adults and are usually fairly distinct events. In children, however, disease complicates the initial infection, so the two stages are on a continuum, often with indistinct borders (2, 6). This lack of clarity can cause confusion when deciding which treatment regimen to use. The current consensus in the United States is to consider disease to be present if adenopathy or other chest radiograph manifestations of infection by *M. tuberculosis* can be seen.

EPIDEMIOLOGY

Disease and Infection

Because most children with tuberculosis infection and disease acquired the organism from an adult in their environment, the epidemiology of childhood tuberculosis tends to follow that in adults. The risk of a child acquiring tuberculosis infection is environmental, determined by the likelihood she will be in contact with an adult with contagious tuberculosis. In contrast, the risk of a child developing tuberculosis disease depends more on host immunologic and genetic factors.

It is estimated that the worldwide annual burden of tuberculosis disease in children is 1 million cases and 210,000 deaths (7–9). The WHO publishes annual reports with estimates of the global burden of tuberculosis disease in children, and, more recently, mathematical models have been implemented to estimate global burden of tuberculosis infection (9–11). The largest number of pediatric patients with tuberculosis is found in Southeast Asia, with India, Indonesia, and Bangladesh comprising three of the four highest-burden countries. In the Western Pacific region, China has the second largest number of newly diagnosed cases of tuberculosis worldwide, while Vietnam has the greatest increase in rates of new diagnoses. Africa has the second largest number of children with tuberculosis, and studies have demonstrated that the proportion of pediatric cases is higher in Sub-Saharan Africa than in any other area of the world (9, 12). Adult tuberculosis case numbers have stayed steady or increased over the past decade in every region of the world except Western Europe. There are no comparable data, but it is likely that childhood tuberculosis has grown in numbers as well.

Between 1953 and 1980, childhood tuberculosis rates in the United States declined about 6% per year. Between 1980 and 1987, the case rates remained relatively flat, but they began to increase in 1988. With improvements in tuberculosis control, rates of childhood tuberculosis started to decline in 1993 and have continued on a downward trend (Fig. 1) (8, 13). In 2015, there were 440 cases in children less than 15 years old (13, 14), a 74% decline since 1993. About 50% of cases occur among infants and children less than 5 years of age. Between the ages of 5 and 14, often called the "favored age," children usually have the lowest rates of tuberculosis disease in any population. The clinical expression of tuberculosis in childhood differs by age (Table 1). Other than meningitis or lymph node disease, other forms of extrapulmonary tuberculosis are more common in older children and adolescents. The gender ratio for tuberculosis in children is about 1:1, in contrast to the ratio in adults, in whom it predominates in males. As with adults, immunocompromising conditions and diabetes mellitus increase the risk of tuberculosis in children (15).

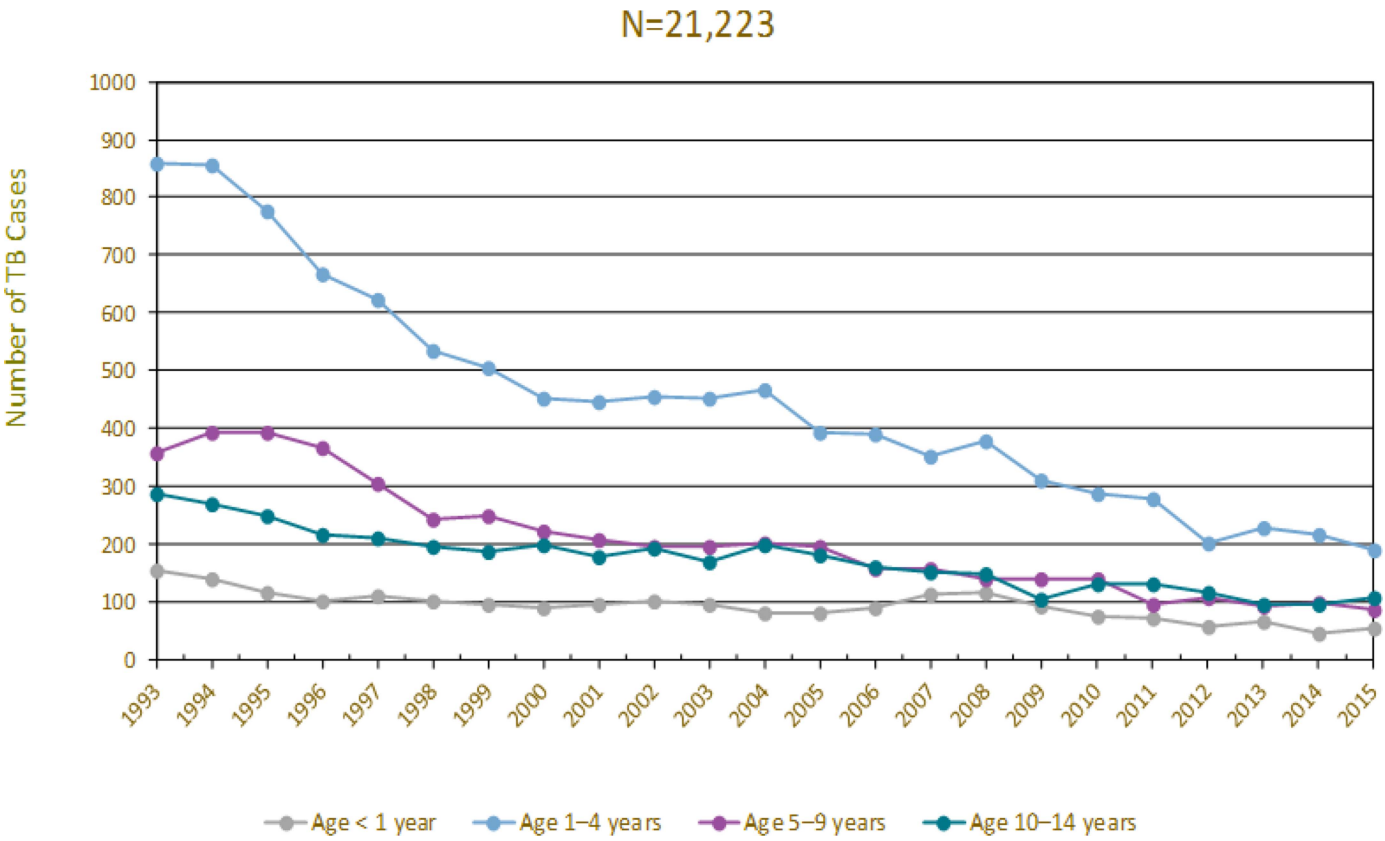


FIGURE 1 Tuberculosis (TB) case rates by age group for children, 1993 to 2015. (Data in the public domain, courtesy of the CDC.)

Childhood tuberculosis is geographically focal in the United States, with several states accounting for 70% of reported cases among children less than 5 years of age (13). As expected, disease rates are highest in cities with more than 250,000 residents.

Childhood tuberculosis case rates in the United States are strikingly higher among ethnic and racial minority groups and the foreign-born than in whites (13, 16). Approximately 88% of cases occur among African American, Hispanic, Asian, and Native American children; this reflects the risk of transmission within the living conditions of these children (13). Most of these children were born in the United States, and the proportion of childhood tuberculosis cases among foreign-born children has been stable at approximately 25%. However, nearly 80% of U.S.-born children with tuberculosis disease have traveled to or had contact with someone who has traveled to a region where tuberculosis is endemic. Foreign-born adoptee children also have high rates of tuberculosis (17–19).

TABLE 1 Childhood tuberculosis cases with any extrapulmonary involvement by age group and selected sites of disease, United States, 1993 to 2015[a]

	% occurrence among children in indicated age group			
Site of disease	<1 yr (*n* = 2,160)	1–4 yrs (*n* = 10,328)	5–9 yrs (*n* = 4,753)	10–14 yrs (*n* = 3,982)
Lymphatic	7.8	19.2	22.3	19.5
Meningeal	8.4	4.0	1.7	2.1
Miliary	4.5	1.1	0.5	1.1
Bone/joint	0.4	1.3	1.8	2.4
Other	3.3	2.6	4.5	9.0
Total	24.4	28.2	30.8	34.2

[a]Provided by the CDC. Data from reference 13.

The recent epidemic of HIV infection has had a profound effect on the epidemiology of tuberculosis among children as a result of two major mechanisms: (i) HIV-infected adults with tuberculosis may transmit *M. tuberculosis* to children, some of whom develop tuberculosis disease (20), and (ii) children with HIV infection may be at increased risk of progressing from tuberculosis infection to disease (21). Several studies of childhood tuberculosis have demonstrated that increased case rates have been associated with a simultaneous increase among HIV-infected adults in the community. In general, HIV-infected children may be more likely to have contact with HIV-infected adults who are at high risk for tuberculosis. Tuberculosis is probably underdiagnosed among HIV-infected children for three reasons: (i) the similarity of its clinical presentation to other opportunistic infections and AIDS-related conditions, (ii) the difficulty in confirming the diagnosis with positive cultures, and (iii) a high mortality rate in poor countries, where tuberculosis may go unrecognized. Children with tuberculosis disease should have HIV serotesting done because the two infections are linked epidemiologically, and HIV-infected children often have more severe manifestations of tuberculosis.

Although data on tuberculosis disease in children are readily available, data concerning tuberculosis infection without disease (positive skin test or IGRA) are lacking. In developing countries where tuberculosis is common, tuberculosis infection rates among the young population average 20 to 50%. However, reliable estimates in these areas are difficult to obtain due to lack of resources, leading to underdiagnosis and underreporting of childhood tuberculosis cases. The worldwide annual burden of tuberculosis infection is unknown; however, a mathematical modeling study estimates that 67,000,000 children under the age of 15 are infected (10). In the United States, tuberculosis infection is a reportable condition in only some states, and national surveys were discontinued in 1971. In most U.S. children, the risk of acquiring tuberculosis infection is less than 1%, but in some urban populations, the risk is much higher, as high as 10%. Most children are infected with *M. tuberculosis* in the home, but outbreaks of childhood tuberculosis infection and disease still occur in elementary and high schools, nursery schools, family day care homes, churches, school buses, and stores. A high-risk adult working in the area has been the source of the outbreak in most cases. The most efficient method of finding children infected with *M. tuberculosis* is through contact investigations of adults with contagious pulmonary tuberculosis. On average, 30 to 50% of all household contacts of an index case have a positive test of infection.

Transmission

Children usually are infected by an adult or adolescent in the immediate household, most often a parent, grandparent, older sibling, or boarder. Casual extrafamilial contact is the source of infection much less often, but babysitters, schoolteachers, music teachers, school bus drivers, parishioners, nurses, gardeners, and candy store keepers have been implicated in individual cases and in hundreds of miniepidemics within limited population groups (22). One study conducted at Texas Children's Hospital found that when chest X rays were routinely obtained for adult caretakers for children admitted to the hospital with suspected tuberculosis, 15% had previously undetected contagious pulmonary tuberculosis (23). Within the household of an infectious adult, the infants and toddlers frequently are infected. Also at high risk are the adolescents, whereas children between 6 and 12 years of age more often escape infection. Adults with pulmonary disease who are receiving regular, appropriate chemotherapy probably rarely infect children; much more dangerous are those with chronic tuberculosis disease that is unrecognized, inadequately treated, or in relapse because of development of resistance.

Wallgren (24), based on studies in orphanages, was the first to point out that children with tuberculosis rarely, if ever, infect other children. Those few children who have transmitted *M. tuberculosis* have the characteristics typical of adult-type tuberculosis (25). Many children with tuberculosis have tuberculin-negative siblings and parents. Children with tuberculosis often have been cared for by their families or in hospitals and institutions without infecting their contacts (23, 26). When transmission of *M. tuberculosis* has been documented in children's hospitals, it almost invariably has come from an adult with undiagnosed pulmonary tuberculosis (27–29). In tuberculous children, tubercle bacilli in endobronchial secretions are relatively sparse, and productive cough is not characteristic of endothoracic tuberculosis or of miliary disease (30). When young children cough, they lack the tussive force of adults. Guidelines issued by the CDC state that most children with typical childhood tuberculosis do not require isolation in the hospital unless they have an uncontrolled productive cough, a cavitary lesion, or sputum smears positive for acid-fast organisms (31). Adolescents with typical reactivation-type pulmonary tuberculosis may be as contagious as adults. Children nevertheless play an extremely important role in the transmission of tuberculosis, not so much because they are likely to contaminate their immediate environment but rather because they harbor a partially healed infection that lies dormant,

only to reactivate as contagious pulmonary tuberculosis many years later under the social, emotional, and physiologic stresses arising during adolescence, pregnancy, or old age. Thus, children infected with *M. tuberculosis* constitute a long-lasting reservoir of tuberculosis in the population.

The risk of infection for child contacts of adults receiving antituberculosis chemotherapy often is a matter of practical concern. Several studies have revealed that most childhood contacts are infected by the index case before diagnosis and the start of treatment. Although it is not possible to carry out a definitive clinical study, evidence indicates that patients on effective chemotherapy rarely transmit *M. tuberculosis*. Nevertheless, it seems prudent to avoid exposing additional children to adults with positive sputum smears or positive cultures and to assume that adults positive by smear or culture remain infectious for at least 2 weeks after the start of effective chemotherapy.

PATHOGENESIS AND IMMUNOLOGY IN CHILDREN

The primary complex of tuberculosis consists of local disease at the portal of entry and the regional lymph nodes that drain the area of the primary focus. The portal of entry is the lung in more than 95% of cases. Tubercle bacilli within particles larger than 10 μm usually are caught by the mucociliary mechanisms of the bronchial tree and are expelled. Small particles are inhaled beyond these clearance mechanisms. However, primary infection may occur anywhere in the body. Ingestion of milk infected with bovine tuberculosis can lead to a gastrointestinal primary lesion. Infection of the skin or mucous membrane can occur through an abrasion, cut, or insect bite. The number of tubercle bacilli required to establish infection in children is unknown, but only several organisms are probably necessary.

The incubation period in children between the time the tubercle bacilli enter the body and the development of cutaneous hypersensitivity is usually 2 to 12 weeks, most often 4 to 8 weeks. The onset of hypersensitivity may be accompanied by a febrile reaction that lasts from 1 to 3 weeks. During this phase of intensified tissue reaction, the primary complex may become visible on chest radiograph. The primary focus grows larger during this time but does not yet become encapsulated. As hypersensitivity develops, the inflammatory response becomes more intense and the regional lymph nodes often enlarge. The parenchymal portion of the primary complex often heals completely by fibrosis or calcification after undergoing caseous necrosis and encapsulation. The parenchymal lesion occasionally enlarges, resulting in focal pneumonitis and thickening of the underlying pleura. If caseation is intense, the center of the lesion may liquefy, empty into the associated bronchus, and leave a residual primary tuberculous cavity.

Tubercle bacilli from the primary complex spread via the bloodstream and lymphatics to many parts of the body during the development of the parenchymal lesion and the accelerated caseation brought on by the development of hypersensitivity. The areas most commonly seeded are the apices of the lungs, liver, spleen, meninges, peritoneum, lymph nodes, pleura, and bone. This dissemination can involve either large numbers of bacilli, which leads to disseminated (miliary) tuberculosis disease, or small numbers of bacilli that leave microscopic tuberculous foci scattered in various tissues. These metastatic foci are clinically inapparent initially, but they are the origin of both extrapulmonary tuberculosis and reactivation pulmonary tuberculosis in some children and many adults.

The tubercle foci in the regional lymph nodes develop some fibrosis and encapsulation, but healing is usually less complete than in the parenchymal lesions. Viable *M. tuberculosis* may persist for decades after calcification of the nodes. The lymph nodes remain normal in size in most cases of primary tuberculosis infection. However, because of their location, hilar and paratracheal lymph nodes that become enlarged by the host inflammatory reaction may encroach upon the regional bronchus. Partial obstruction caused by external compression leads at first to hyperinflation in the distal lung segment. Such compression may occasionally cause complete obstruction of the bronchus, resulting in atelectasis of the lung segment (2, 32, 33). More often, inflamed caseous nodes attach to the bronchial wall and erode through it, leading to endobronchial tuberculosis or a fistulous tract. The extrusion of infected caseous material into the bronchus can transmit infection to the lung parenchyma and cause bronchial obstruction and atelectasis. The resultant lesion is a combination of pneumonia and atelectasis. The radiographic findings of this process have been referred to as "epituberculosis," "collapse-consolidation," and "segmental" tuberculosis. Rarely, tuberculosis intrathoracic lymph nodes invade other adjacent structures, such as the pericardium or esophagus.

A fairly predictable timetable for primary tuberculosis infection and its complications in infants and children is apparent (34). Massive lymphohematogenous dissemi-

nation leading to meningitis, miliary, or disseminated disease occurs in 0.5 to 2% of infected children, usually no later than 2 to 6 months after infection. Clinically significant lymph node or endobronchial tuberculosis usually appears within 3 to 9 months. Lesions of the bones and joints usually take at least a year to develop; renal lesions may be evident 5 to 25 years after infection. In general, intrathoracic complications of the primary infection occur within the first year.

Tuberculosis disease that occurs more than a year after the primary infection is thought to be secondary to endogenous regrowth of persistent bacilli from the primary infection and subclinical dissemination. Exogenous reinfection may result in tuberculosis disease in rare cases, but most cases of postprimary or reactivation tuberculosis in adolescents are believed to be secondary to endogenous organisms. Reactivation tuberculosis is rare in infants and young children. Reactivation tuberculosis among adolescents affects females twice as often as males for unknown reasons. The most common form of reactivation tuberculosis is an infiltrate or cavity in the apex of the lung, where oxygen tension is high and there is a heavy concentration of tubercle bacilli deposited during the primary subclinical dissemination of organisms. Dissemination during reactivation tuberculosis is rare among immunocompetent adolescents.

The age of the child at acquisition of tuberculosis infection seems to have a great effect on the occurrence of both primary and reactivation tuberculosis. Hilar lymphadenopathy and subsequent segmental disease complicating the primary infection occur most often in younger children. Approximately 50% of untreated children less than 1 year of age develop radiographically significant lymphadenopathy or segmental lesions, compared with 24% of children 1 to 10 years of age and 16% of children 11 to 15 years of age (35). However, if young children do not suffer early complications, their risk of developing reactivation tuberculosis later in life appears to be quite low. Conversely, older children and adolescents rarely experience complications of the primary infection but have a much higher risk of developing reactivation pulmonary tuberculosis as an adolescent or adult.

Although protective immunity to tuberculosis in children is incompletely understood, several key attributes have been identified. As evidenced by children with underlying immunodeficiency, immune control of mycobacteria is dependent upon cell-mediated immunity (*M. tuberculosis*-specific T lymphocytes, dendritic cells, Toll-like receptors, IFN-γ, tumor necrosis factor alpha, and interleukin 2), as well as macrophages and neutrophils (36). Additionally, there is a distinctive risk profile of tuberculosis among children; younger children and adolescents are at higher risk of progressing from infection to disease than children between 5 and 10 years old. The precise changes to the immune system responsible for this risk profile are yet to be determined, although insufficient production and function of Toll-like receptors, dendritic cells, and macrophages, as well as a deficient ability for CD4 cells to express Th1 effector function, likely impact the higher risk of disease progression in neonates and young infants. As immune maturation proceeds, the risk for progressing to disease decreases (37, 38).

CLINICAL MANIFESTATIONS

How Children with Tuberculosis Are Discovered

In the high-tuberculosis-burden countries, the predominant way children with tuberculosis disease are discovered is passively when they present with an illness that is consistent with tuberculosis (39). Having an ill adult contact is an obvious clue to the correct diagnosis. The only available laboratory test may be an acid-fast smear of sputum or the GeneXpert MTB/RIF PCR assay (Xpert) (Cepheid Inc. Sunnyvale, CA), but both are positive in fewer than 20% of childhood tuberculosis cases. Chest radiography is not available in many high-burden countries. To aid in diagnosis, a variety of clinical scoring systems have been devised based on available tests, clinical signs and symptoms, and known exposures. However, the sensitivity and specificity of these systems can be very low, leading to both over- and underdiagnosis of tuberculosis (40). No clinical scoring system has been validated in a clinical trial. Ironically, childhood tuberculosis is often most difficult to accurately diagnose where the incidence is highest.

In 2013, the WHO developed guidelines which several countries have implemented for intensified case finding strategies for childhood tuberculosis (active-case finding) in high-burden countries (41). Recommendations include screening those who have had close contact with someone with tuberculosis, individuals who are infected with HIV, and those with poor access to health care. For children, there are a variety of screening algorithms, though this is primarily done via interviews regarding tuberculosis symptomatology and HIV status (42). Studies investigating active-case finding strategies have demonstrated that they improve rates of diagnosis, allow for earlier diagnosis, and are cost-effective (43, 44).

In low-burden countries, children with tuberculosis usually are discovered in one of three ways (45).

Obviously, one way is consideration of tuberculosis as the cause of a symptomatic pulmonary or extrapulmonary illness. Discovering an adult contact with infectious tuberculosis is an invaluable aid to diagnosis; the "yield" from contact investigation usually is higher than that from cultures from the child. The second way is discovery of a child with pulmonary tuberculosis during the contact investigation of an adult with tuberculosis. The affected child typically has few or no symptoms, but investigation reveals a positive test of infection and an abnormal chest radiograph. Up to 50% of children with pulmonary tuberculosis are discovered in this manner in some areas of the United States before significant symptoms have begun. In the third way, a smaller number of children with tuberculosis disease are found as the result of a community- or school-based testing program for tuberculosis infection or disease.

Pulmonary Disease

The symptoms and physical signs of intrathoracic tuberculosis in children are surprisingly meager considering the degree of radiographic changes often seen. The physical manifestations of disease tend to differ by the age of onset. Young infants are more likely to have significant signs or symptoms (46).

In the United States, about one-half of infants and children with radiographically moderate to severe pulmonary tuberculosis have no physical findings and are discovered only via contact tracing of an adult with tuberculosis. The chest radiograph typically is "sicker" than the child. Infants are more likely to experience signs and symptoms, probably because of their small airway diameters relative to the parenchymal and lymph node changes in primary tuberculosis (Table 2). Nonproductive cough and mild dyspnea are the most common symptoms. Systemic complaints such as fever, night sweats, anorexia, and decreased activity (malaise) occur less often. Some infants have difficulty gaining weight and develop a failure-to-thrive presentation that often does not improve significantly until after several months of treatment.

TABLE 2 Symptoms and signs of childhood pulmonary tuberculosis

Symptom or sign	Occurrence in:	
	Infants and young children	Older children and adolescents
Fever	Common	Uncommon
Night sweats	Rare	Uncommon
Cough	Common	Common
Productive cough	Rare	Common
Hemoptysis	Never	Rare
Dyspnea	Common	Rare
Rales	Common	Uncommon
Wheezing	Common	Uncommon
Dullness	Rare	Uncommon
Diminished breath sounds	Common	Uncommon

Pulmonary signs are even less common. Some infants and young children with bronchial obstruction show signs of air trapping, such as localized wheezing or decreased breath sounds that may be accompanied by tachypnea or frank respiratory distress. These nonspecific symptoms and signs are occasionally alleviated by antibiotics, suggesting that bacterial superinfection distal to the focus of tuberculous bronchial obstruction contributes to the clinical presentation of disease.

A rare but serious complication of primary tuberculosis in children occurs when the parenchymal focus enlarges and develops a caseous center (47). The radiographic and clinical picture of progressive primary tuberculosis is that of bronchopneumonia with high fever, moderate to severe cough, night sweats, dullness to percussion, rales, and decreased breath sounds. Liquefaction in the center may result in formation of a thin-walled cavity (48, 49). The enlarging focus may slough debris into adjacent bronchi, leading to intrapulmonary dissemination. Rupture of the cavity into the pleural space may cause a bronchopleural fistula or pyopneumothorax, rupture into the pericardium can cause acute pericarditis with constriction, and rupture into the esophagus can create a tracheoesophageal fistula. Before the advent of antituberculosis chemotherapy, the mortality rate of progressive primary pulmonary tuberculosis was 30 to 50%. Currently, with effective treatment, the prognosis is excellent.

Older children and adolescents, especially those with reactivation-type tuberculosis, are more likely to experience fever, anorexia, malaise, weight loss, night sweats, productive cough, chest pain, and hemoptysis than children with primary pulmonary tuberculosis (50–52). However, findings on physical examination are usually minor or absent even when cavities or large infiltrates are present. Most signs and symptoms improve within several weeks of starting effective treatment, although cough may last for several months.

As expected, the radiographic findings in childhood tuberculosis reflect the pathophysiology and are quite different from findings in adults (Table 3) (53). The hallmark of primary pulmonary tuberculosis is the relatively large size and importance of the lymphadenitis

TABLE 3 Comparison of chest radiographs of pulmonary tuberculosis in adults and children

Characteristic(s)	Occurrence in:	
	Adults	Children
Location	Apical	Anywhere (25% multilobar)
Adenopathy	Rare (except HIV related)	Usual
Cavitation	Common	Rare (except adolescent)
Signs and symptoms	Consistent	Relative paucity

compared with the less significant size of the initial parenchymal focus. Because of the usual pattern of lymphatic circulation within the lungs, a left-sided parenchymal focus often leads to bilateral hilar adenopathy, while a right-sided focus is associated only with right-sided lymphadenitis. Hilar and/or mediastinal lymphadenopathy is invariably present with childhood tuberculosis but may not be distinct (from the atelectasis and infiltrate) or may be too small to be seen clearly on a plain radiograph. Computed tomography (CT) may reveal small lymph nodes when the chest radiograph is normal, but this finding appears to have no clinical implications (54). It can, however, create a dilemma in deciding on a treatment regimen and reinforces the idea that in children, infection and disease are on a continuum with often indistinct borders (6).

In most cases of tuberculosis infection in children, the initial mild parenchymal infiltrate and lymphadenitis resolve spontaneously and the chest radiograph is normal. In some children, the hilar or mediastinal lymph nodes continue to enlarge. Partial airway obstruction caused by external compression from the enlarging nodes causes air trapping and hyperinflation. As the nodes attach to and infiltrate the airway, caseum filling the lumen causes complete obstruction, resulting in atelectasis that involves the lobar segment distal to the obstructed lumen (Fig. 2). The resulting radiographic shadows are called collapse-consolidation or segmental lesions (Fig. 3 and 4). These findings resemble those in foreign body aspiration; in the case of tuberculosis, the lymph node is acting as the foreign body. Multiple segmental lesions in different lobes may appear simultaneously, as can atelectasis and hyperinflation.

Other radiographic findings are noted in some children. Occasionally, children have a lobar pneumonia without distinct hilar adenopathy. In infants and young children, the radiographic appearance can resemble exudative pneumonia, similar to that caused by *Klebsiella pneumoniae* or *Staphylococcus aureus* (Fig. 5). A secondary bacterial pneumonia may contribute to

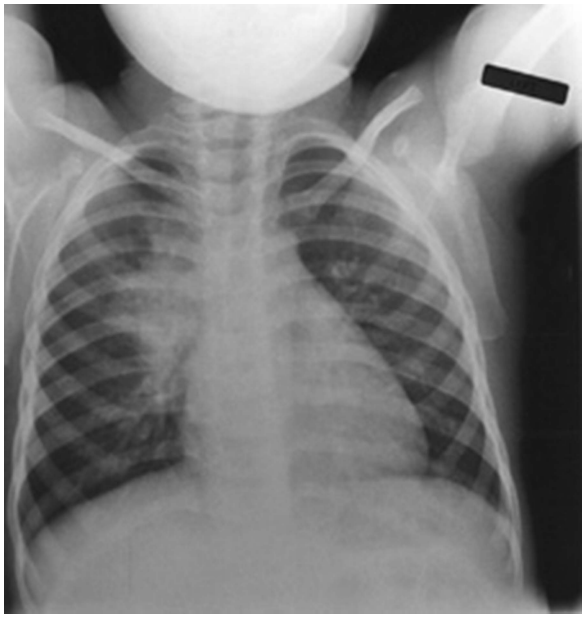
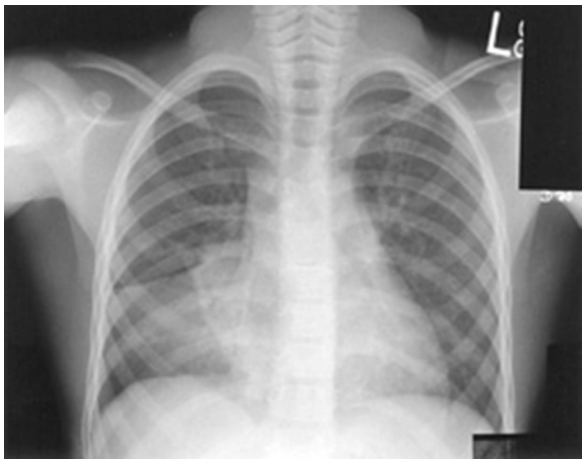


FIGURE 2 Early collapse-consolidation lesion in a child with tuberculosis. Mediastinal adenopathy also is present on the right side.

this appearance. When tuberculosis infection is progressively destructive, liquefaction of lung parenchyma leads to formation of a thin-walled primary tuberculosis cavity. Peripheral bullous lesions occur rarely and can lead to pneumothorax (55). Enlargement of subcarinal nodes causes compression of the esophagus, difficulty swallowing, and, rarely, a bronchoesophageal fistula. One sign of early subcarinal tuberculosis is horizontal splaying of the mainstem bronchi.

Adolescents with pulmonary tuberculosis may develop segmental lesions with associated adenopathy,

FIGURE 3 Slightly more extensive right-sided adenopathy with atelectasis in a 2-year-old with tuberculosis.



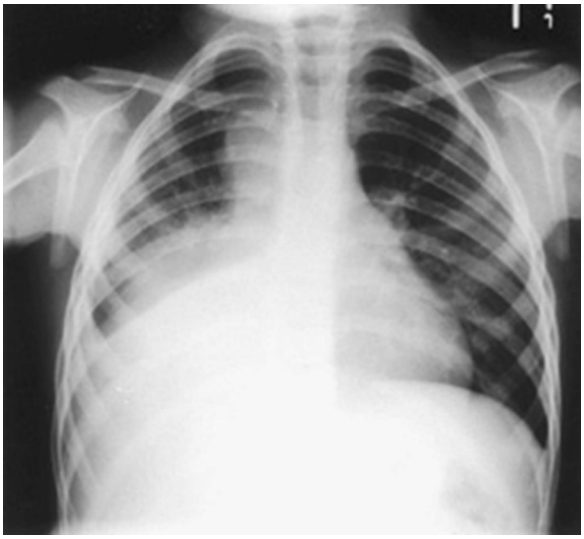


FIGURE 4 Well-formed collapse-consolidation lesion on the right, with large mediastinal and hilar adenopathy and atelectasis.

but more often, they develop the infiltrates with or without cavitation that are typical of adult reactivation tuberculosis (Fig. 6) (50, 56). The lesions are often smaller in adolescents than in adults, and lordotic views, tomograms, or even a CT scan may be necessary to demonstrate small apical foci of disease.

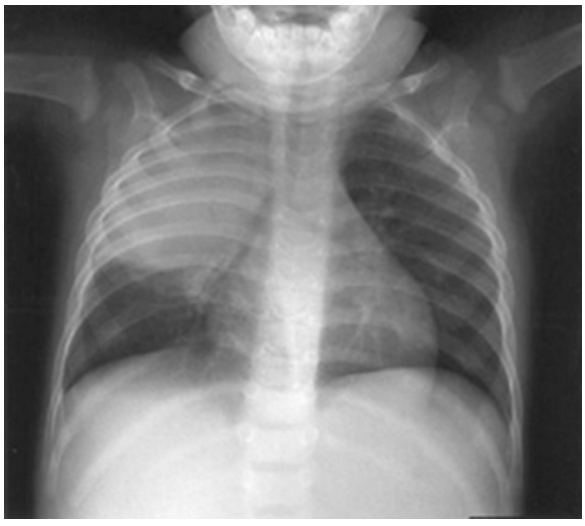
The course of thoracic lymphadenopathy and bronchial obstruction can follow several paths. The segment of lobe reexpands in most cases, and the radiographic abnormalities resolve completely. The resolution occurs slowly, over months to several years, and is not affected greatly by antituberculosis therapy. Of course, children still have infection with *M. tuberculosis* and are at high risk of reactivation tuberculosis in subsequent years if chemotherapy has not been taken. In some cases, the segmental lesion resolves but residual calcification occurs in the primary parenchymal focus or regional lymph nodes. The calcification usually occurs in fine particles, creating a stippling effect. Calcification begins 6 months or more after infection. Even with chemotherapy, the enlarged lymph nodes and endobronchial lesions may persist for many months, occasionally resulting in severe airway obstruction. Surgical or endoscopic removal of intraluminal lesions is rarely necessary. Finally, bronchial obstruction may cause scarring and progressive contraction of the lobe or segment, which is often associated with cylindrical bronchiectasis. Complete radiographic and clinical resolution without calcification occurs in the vast majority of cases with early institution of adequate treatment for collapse-consolidation lesions.

Pleural Disease

Tuberculous pleural effusions, which can be local or general, usually originate in the discharge of bacilli into the pleural space from a subpleural pulmonary focus or caseated subpleural lymph nodes (57). Asymptomatic local pleural effusion is so frequent in primary tuberculosis that it is basically a component of the primary complex. Most large and clinically significant effusions occur months to years after the primary infection (Fig. 7). Tuberculous pleural effusion is less common in children younger than 6 years of age and rare in those below 2 years of age (58). Such effusions are usually unilateral but can be bilateral. They are virtually never associated with a segmental pulmonary lesion and are rare in miliary tuberculosis.

The clinical onset of tuberculous pleurisy in children is usually fairly sudden, with low to high fever, shortness of breath, chest pain (especially on deep inspiration), dullness to percussion, and diminished breath sounds on the affected side. The presentation is similar to that of pyogenic pleurisy. The fever and other symptoms may last for several weeks after the start of antituberculosis chemotherapy. Although corticosteroids may reduce the clinical symptoms, they have little effect on the ultimate outcome. The TST is positive in only 70 to 80% of cases, and Xpert has shown poor sensitivity for diagnosis of pleural tuberculosis (59). However, a recent meta-analysis demonstrated that IGRAs performed on pleural fluid have improved sensitivity compared to that of IGRAs performed on blood and may be used as a complementary test for diagnosing tuberculous pleurisy

FIGURE 5 Tuberculous pneumonia with bowing of the horizontal fissure. Children with this finding may have an associated bacterial infection.



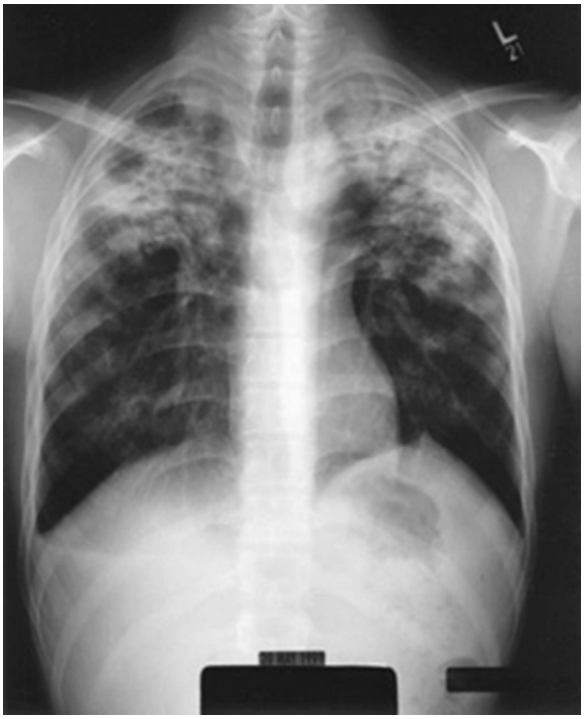


FIGURE 6 Reactivation-type tuberculosis in an adolescent boy.

(60). The prognosis of pleural tuberculosis in children is excellent, but complete radiographic resolution can take months. However, scoliosis rarely complicates recovery of a long-standing effusion.

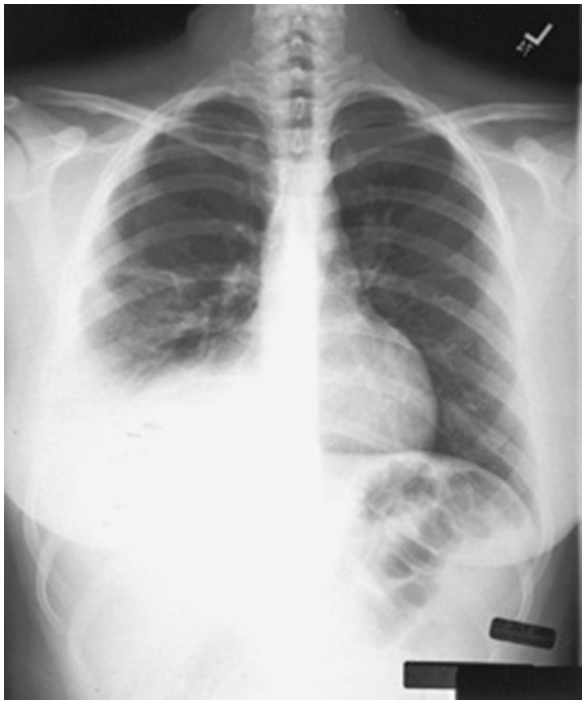
Extrathoracic Tuberculosis

The various forms of extrapulmonary tuberculosis are reviewed in detail in other chapters. Up to 25 to 35% of childhood tuberculosis cases are extrapulmonary (Table 1), and a careful physical examination is an essential component of the evaluation of a child with tuberculosis exposure or infection. The most common location of extrapulmonary tuberculosis in children is the lymph nodes of the neck (61–63).

The two forms of extrapulmonary tuberculosis that receive the most attention, because of their life-threatening nature, are disseminated (miliary) disease (Fig. 8) and meningitis. Both forms of disease occur early, often within 2 to 6 months of initial infection. Correct diagnosis requires a high index of suspicion because it is difficult to confirm these diseases microbiologically (64, 65). Acid-fast stains of body fluids are almost always negative; cultures for *M. tuberculosis* are positive in only 50% of cases or fewer, and they often take weeks to grow because the initial inoculum of organisms is so low (64, 66–69). In addition, the TST and IGRAs may be nonreactive initially for up to 50% of pediatric patients, and the chest radiograph in both diseases may be normal early on. The key element to correctly diagnose each condition is an epidemiologic history, a search for the adult from whom the child acquired *M. tuberculosis*. Unfortunately, an initial negative history for exposure does not really help. In a study of 31 consecutive infants and children with central nervous system tuberculosis in Houston, TX, the initial family history was negative for tuberculosis in 30 cases, although the adult source case was ultimately identified in over 60% of cases (70). The ill adult often has not yet been diagnosed correctly because the incubation period of disseminated tuberculosis and meningitis in children may be short. An evaluation of the family and other adults and adolescents in close contact with the child should be considered a public health emergency when serious tuberculosis disease is suspected in a child.

The most feared complication of tuberculosis in children is meningitis (71). Meningitis is the most common cause of morbidity and mortality due to tuberculosis in children. The mortality rate is often 50% in high-burden countries, and up to 75% of those who survive have lasting neurologic sequelae (66, 72). The peak incidence occurs in children aged 2 to 4 years, and though the pathogenesis is incompletely understood, it frequently occurs as part of disseminated disease (72, 73). Although

FIGURE 7 A tuberculous pleural effusion in an adolescent girl.



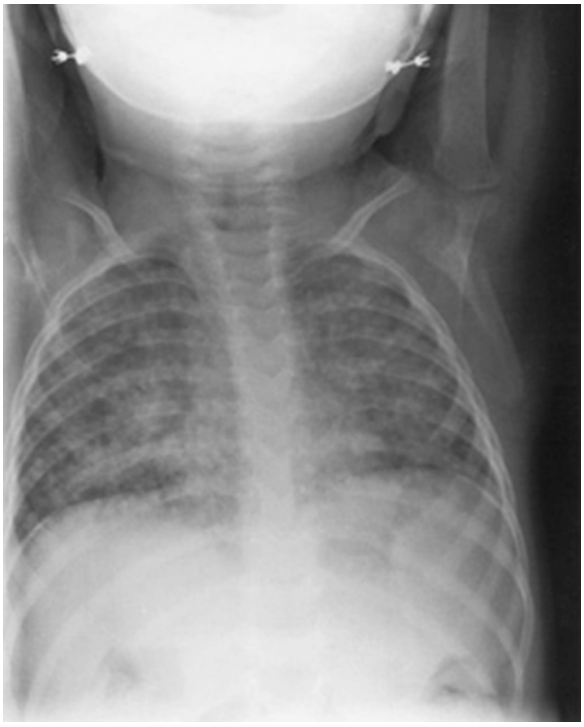
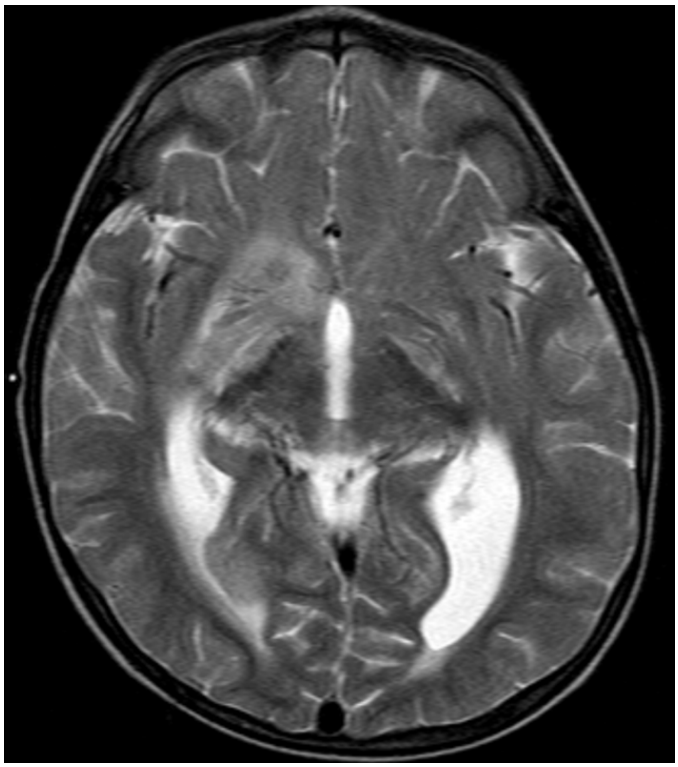


FIGURE 8 Miliary tuberculosis in an infant. The child presented with fever and respiratory distress.

the clinical onset of tuberculous meningitis in children may occur over several weeks, recent studies describe more rapid progression over several days. Early on, the clinical presentation may be similar to that of viral or pyogenic meningitis. However, tuberculous meningitis in children is more likely to be complicated by cranial nerve involvement, basilar leptomeningeal involvement, hydrocephalus, and infarct caused by vasculitis. These findings in any child with meningitis, when no other cause is readily apparent, should prompt immediate initiation of antituberculosis chemotherapy while diagnostic studies and investigation of close contacts for tuberculosis are carried out as quickly as possible.

Complications of tuberculous meningitis include deafness, visual disturbances, seizures, hydrocephalus, ischemic brain injury, and tuberculomas (72, 74). Hydrocephalous can be either communicating or obstructive (typically cerebrospinal fluid [CSF] flow is blocked from exiting the fourth ventricle) and can lead to increased intracranial pressure (72) caused by infarct or development of a tuberculoma. The widespread use of improved cranial imaging, such as CT scan and magnetic resonance imaging, has shown that tuberculoma is more common than previously realized, and the distinction in children between tuberculous meningitis and tuberculoma is not as clear as once thought. Tuberculomas account for up to 40% of brain tumors in children in some developing countries. They often occur in children less than 10 years of age, may be single or multiple, and are often located at the base of the brain, near the cerebellum (Fig. 9). However, a recently recognized phenomenon is the paradoxical development of intracranial tuberculomas appearing or enlarging during treatment of meningeal, disseminated, and even pulmonary tuberculosis (75, 76). This phenomenon appears to be similar to the well-described worsening of intrathoracic adenopathy seen in many children during the first few months of ultimately successful chemotherapy for tuberculosis. The tuberculomas seem to be mediated immunologically; they respond (slowly) to corticosteroid therapy, and a change in antituberculosis therapy is not required. Some infants with pulmonary tuberculosis and very subtle neurologic signs or symptoms have one or several tuberculomas, even with a normal CSF evaluation. Any neurologic abnormality in a child with suspected pulmonary tuberculosis should be evaluated with a neuroimaging study when feasible (70).

FIGURE 9 Magnetic resonance imaging showing abnormal enhancement along the basilar cisterns, acute ischemia or possibly cerebritis involving the right caudate head, right putaminal and possibly right globus pallidus, ventriculomegaly (ventriculoperitoneal shunt in place), and enhancement along multiple cranial nerves.



Tuberculosis in HIV-Infected Children

HIV is a significant risk factor for the development of tuberculosis disease. There are limited data on incidence rates of tuberculosis in HIV-infected children, and rates vary significantly depending on the prevalence of HIV and tuberculosis in the community (77). A study conducted in South Africa demonstrated that the incidence of tuberculosis in HIV-infected children was 42 times that in HIV-uninfected children (78). Infants infected with HIV are at particularly high risk for developing tuberculosis (79).

In adults infected with both HIV and *M. tuberculosis*, the rate of progression from asymptomatic infection to disease is increased greatly (21, 80). The mechanisms for this, though, are not fully understood. The risk of progression from infection to disease increases with depletion of CD4 T cells; however, studies demonstrate that individuals infected with HIV who are on antiretroviral therapy (ART) or who are recently infected with HIV and still have high CD4 T cell counts are at increased risk for developing tuberculosis disease (77). The clinical manifestations of tuberculosis in HIV-infected adults tend to be typical when the $CD4^+$ cell count is more than 500 per mm3 but become "atypical" as the $CD4^+$ cell count falls. Similar correlations have not been reported for dually infected children. When HIV-infected children develop tuberculosis, the clinical features tend to be fairly typical of disease in immunocompetent children, although the disease often progresses more rapidly, and clinical manifestations are more severe (81–83). There may be an increased tendency for extrapulmonary disease, but the trend is not as dramatic as it is in HIV-infected adults (21). Unfortunately, higher mortality rates have been noted, including those from other AIDS-related conditions, if effective ART is not also given (84). The diagnosis of tuberculosis in an HIV-infected child can be difficult to establish, as the two infections have multiple manifestations which overlap, skin test reactivity may be absent, IGRAs are less sensitive, culture confirmation is slow and difficult, and the clinical presentation may be similar to that of other HIV-related infections and conditions (77, 85). A diligent search for an infectious adult in the child's environment often yields the strongest clue to the correct diagnosis. To aid in confirming the diagnosis, the WHO recommends use of the Xpert assay for *M. tuberculosis* for patients with HIV infection, as prospective studies have shown improved sensitivity of this test compared with that of sputum microscopy (86, 87). HIV-infected patients being treated for tuberculosis can experience a worsening of signs and symptoms if concomitant ART causes a rapid decrease in HIV load and an increase in $CD4^+$ cell counts. The immune reconstitution inflammatory syndrome has been observed in children being treated for tuberculosis and in children who have received a *Mycobacterium bovis* Bacillus Calmette–Guérin (BCG) vaccine (88–90). The most common manifestations are at the anatomic site of the existing tuberculosis, but new onset of tuberculomas, lymphadenopathy, and abdominal manifestations can occur (74, 91, 92). Immune reconstitution inflammatory syndrome should be suspected when an HIV-infected child develops apparent complications of tuberculosis (or BCG vaccination) after starting ART, though other potential causes should be considered.

DIAGNOSIS

Tuberculin Skin Test

The TST has been reviewed extensively in a previous chapter. The placement of the Mantoux intradermal skin test, while fairly simple and routine in a cooperative adult, can be a challenge in a squirming, scared child. The technique shown in Fig. 10 allows for better control during placement. The skin tester anchors her hand along the longitudinal axis of the child's arm, which enhances stability and allows the last two fingers to become a fulcrum to guide inoculation of the solution. The tuberculin is injected laterally across the arm. As with adults, a wheal of 6 to 10 mm should be raised after injection. The test is interpreted at 48 to 72 h after placement. Although recent formal studies are lacking,

FIGURE 10 A helpful technique for applying the Mantoux TST on a child. The hand is anchored on the side of the child's arm, providing stability. The tuberculin is injected in a lateral direction.

most experts believe that the time course of the reaction and amount of induration produced are similar in children and adults. Infants may make slightly less induration, on average, when infected.

The interpretations of the Mantoux skin test should be similar in children and adults (93–95). However, most of the "risk factors" for children are actually the risk factors of the adults in their environment, i.e., the likelihood that the child has had significant contact with an adult with contagious pulmonary tuberculosis. Correctly classifying a child's reaction supposes that the risk factors of the adults around the child have been considered. The American Academy of Pediatrics (AAP) has suggested that 10 mm should be the cutoff point for all children less than 4 years of age (96). This recommendation is not based on diminished ability to make an induration reaction in children; it was made to minimize false-negative reactions in small children who are at increased risk of developing life-threatening forms of tuberculosis once infected.

The factors that influence the accuracy of tuberculin skin testing in adults also affect children. About 10 to 20% of children with tuberculosis disease initially have a negative reaction to tuberculin (97, 98). The lack of reactivity may be global or may occur only for tuberculin, so "control" skin tests may be of limited usefulness in children. In most cases (other than those with advanced HIV infection or other ongoing immunosuppression), the reaction becomes positive as the child recovers on chemotherapy. Incubating or manifest viral infections are a frequent cause of false-negative results in children.

Previous inoculation with a BCG vaccination can pose problems with interpretation of a subsequent TST. Although many infants who receive a BCG vaccine never develop a skin test reaction to tuberculin, about 50% do. The reactivity fades over time but can be boosted in children with repeated skin testing (99, 100). Most experts agree that skin test interpretation in children who received a BCG vaccine more than 3 years previously should be the same as if they had never received vaccine, though some false-positive reactions will occur. When skin testing is done sooner after vaccination, interpretation is more difficult. The clinician should have a clear understanding of why the test was placed and realize that a positive reaction most likely represents infection with *M. tuberculosis* if the child had a specific exposure to an infectious adult or adolescent.

IFN-γ Release Assays

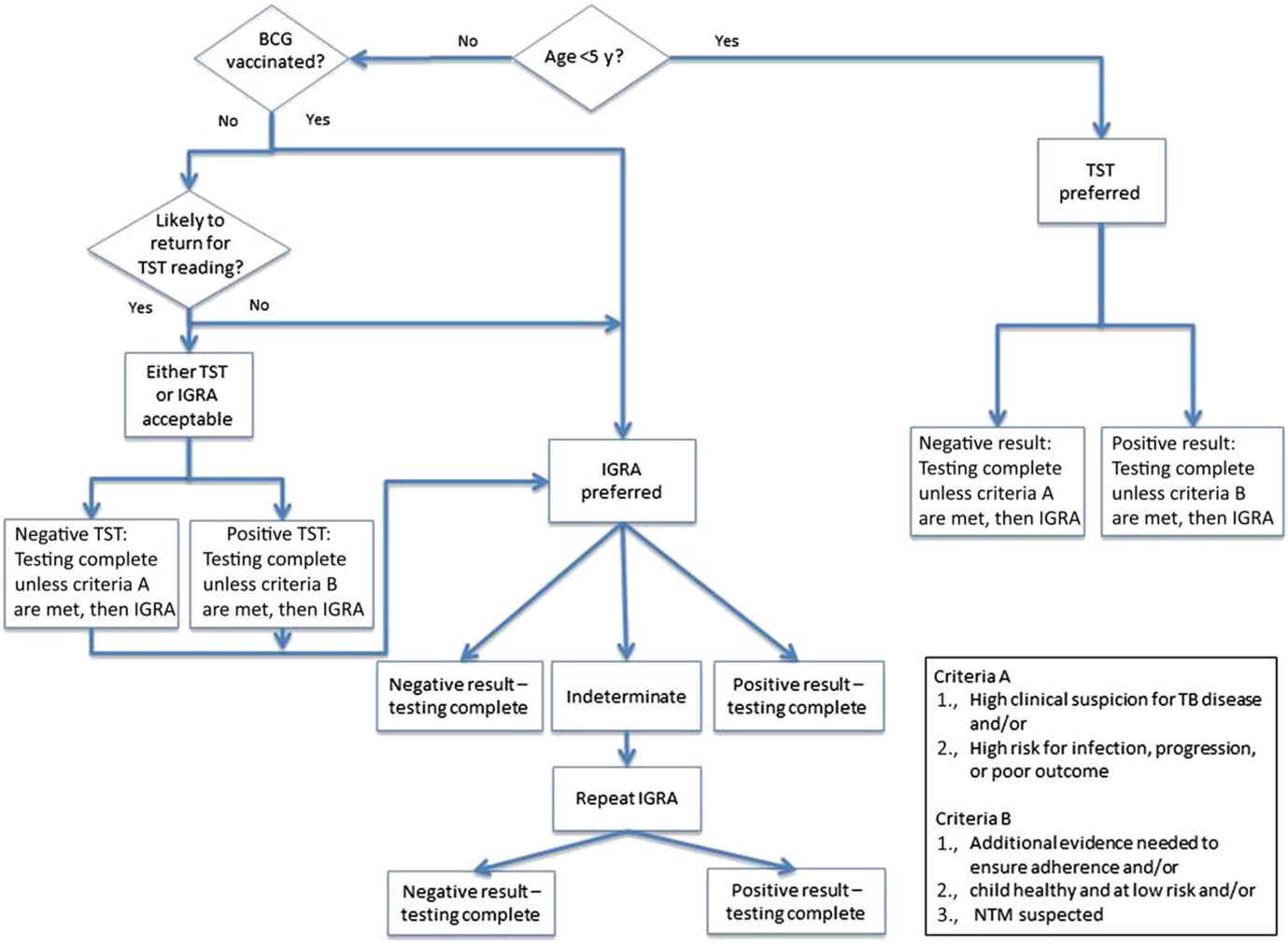
QuantiFERON TB GOLD In Tube (QFT) and T-SPOT. TB (T-SPOT) are IGRAs. These tests measure *ex vivo* IFN-γ production from T lymphocytes in response to stimulation with antigens that are fairly specific to *M. tuberculosis* complex. As with TSTs, IGRAs cannot distinguish between infection and disease, and a negative result from these tests cannot exclude the possibility of tuberculosis infection or disease in a patient with findings that raise suspicion for these conditions. Both tests have positive and negative controls: if the positive control shows a low response or if the negative control shows too high of a response, the result is considered indeterminate (QFT)/invalid (T-SPOT). The QFT is an enzyme-linked immunosorbent assay whole-blood test which quantifies the amount of IFN-γ released, while the T-SPOT measures the number of IFN-γ-producing T cells. There are small differences in outcomes between the two tests, but neither is considered preferred. Multiple meta-analyses comparing IGRAs to TSTs have demonstrated that the sensitivity of these blood tests is similar to that of TSTs for detecting infection in adults and children who have untreated culture-confirmed tuberculosis. The specificity of IGRAs is higher than that for TSTs because the antigens used are not found in BCG or most pathogenic nontuberculous mycobacteria (101–108). The published experience with testing children with IGRAs is less extensive than for adults, but a number of studies have demonstrated that IGRAs perform well for most children 4 years of age and older (107, 109–115). There has been a hesitancy to use IGRAs for children younger than 5 years due to lack of data for test sensitivity, along with the increased likelihood of progression from infection to disease in this age group (107). The few studies conducted among children younger than 5 years have demonstrated that IGRAs have high specificity and concordance with TSTs (116). However, both IGRAs and TSTs have lower sensitivity in this age group, in particular for children younger than 2 years, as well as higher rates of indeterminate or invalid results for the IGRAs (117, 118). Based on current knowledge, if an IGRA result is positive for a child younger than 5 years, she likely has infection with *M. tuberculosis*, but a negative result does not rule out infection (107).

Some children who received BCG vaccine may have a false-positive TST result. However, the correct interpretation of a negative IGRA result in a child with a positive TST result remains challenging because of the current absence of longitudinal studies to determine the negative predictive value of the IGRAs (when the TST result is positive and the IGRA result is negative). The decision to treat should be based on age of the patient, underlying risk factors, and exposure history (107, 119).

Children who are immunocompromised due to HIV infection, malnutrition, malignancy, or immunosuppressive medications are at increased risk of progressing from having tuberculosis infection to disease. Unfortunately, there are limited data describing the sensitivity and specificity of IGRAs in these patient populations. Studies evaluating children infected with HIV have shown that IGRAs are not more sensitive than the TST and there is less concordance with the TST in those with advanced disease (120, 121). A small study with children with cancer demonstrated poor concordance between IGRAs and TST as well as decreased test sensitivity among these patients (122). In children with medical conditions necessitating use of immunosuppressive therapy, immunomodulating biologic agents in particular (such as those with rheumatologic disease or inflammatory bowel disease), screening for tuberculosis infection is particularly important, as patients receiving these medications are at increased risk for having progression from tuberculosis infection to disease (107). Although there are no published studies involving children, based on a limited number of studies with adults, experts suggest the use of either the TST or an IGRA to screen for tuberculosis infection if the patient has no specific risk factors other than the immunosuppressive therapy but the use of both the TST and IGRA if the patient has additional tuberculosis risk factors (107, 123).

At this time, neither an IGRA nor the TST can be considered a gold standard for diagnosis of tuberculosis infection. Current recommendations for use of IGRAs in children are as follows (Fig. 11) (107):

FIGURE 11 An algorithm for the use of the TST and IGRAs in children. Entry into the algorithm assumes that the child has at least 1 risk factor for TB infection. Note: many experts use age <2 years as the starting point. Reprinted from reference 107, with permission from the American Academy of Pediatrics Committee on Infectious Diseases.



- For immunocompetent children 5 years of age and older, IGRAs can be used in place of a TST and is likely to yield fewer false-positive test results.
- Many experts now use IGRAs routinely to test for tuberculosis infection or disease in children down to 2 years of age (107).
- Children with a positive result from an IGRA should be considered infected with *M. tuberculosis* complex. A negative IGRA result cannot universally be interpreted as absence of infection.
- Because of their higher specificity and lack of cross-reaction with BCG, IGRAs may be especially useful for children who have received a BCG vaccine. IGRAs may be useful to determine whether a BCG-immunized child with a reactive TST more likely has tuberculosis infection or has a false-positive TST reaction caused by the BCG.
- Indeterminate (QFT)/invalid (T-SPOT) IGRA results do not exclude tuberculosis infection and should not be used to make clinical decisions.

Diagnostic Mycobacteriology in Children

The demonstration of acid-fast bacilli in stained smears of sputum is presumptive evidence of pulmonary tuberculosis in most patients. However, in children, tubercle bacilli usually are relatively few in number, and sputum cannot be obtained spontaneously from most children younger than about 10 years of age. Gastric washings, which often are used in lieu of sputum, can be contaminated with acid-fast organisms from the mouth. However, fluorescence microscopy of gastric washings has been found useful, though the yield is less than 10% (124, 125).

Tubercle bacilli in CSF, pleural fluid, lymph node aspirate, and urine are sparse; thus, only rarely are direct-stained smears for tubercle bacilli positive in pediatric practice. Cultures for tubercle bacilli are of great importance, not only to confirm the diagnosis but also increasingly to permit testing for drug susceptibility. However, if culture and drug susceptibility data are available from the associated adult case and the child has a classic presentation of tuberculosis (positive skin test or IGRA, consistent abnormal chest radiograph, and exposure to an adult case), obtaining cultures from the child adds little to the management.

Painstaking collection of specimens is essential for culture diagnosis in children because usually fewer organisms are present than in adults. Gastric lavage should be performed in the very early morning, when the patient has had nothing to eat or drink for 8 h and before the patient has a chance to wake up and start swallowing saliva, which dilutes the bronchial secretions that were brought up during the night and made their way into the stomach (126). Inhalation of superheated nebulized saline prior to gastric lavage has been reported to increase the bacteriologic yield (127). The stomach contents should be aspirated first. No more than 50 to 75 ml of sterile distilled water (not saline) should be injected through the stomach tube, and the aspirate should be added to the first collection. The gastric acidity (poorly tolerated by tubercle bacilli) should be neutralized immediately. Concentration and culture should be performed as soon as possible after collection. However, even with optimal, in-hospital collection of three early morning gastric aspirate samples, *M. tuberculosis* can be isolated from only 30% to 40% of children and 70% of infants with pulmonary tuberculosis (46, 95, 124, 128–130). The yield from random outpatient gastric aspirate samples is exceedingly low. Despite their low yield, gastric aspirates have been demonstrated to have better yield than nasopharyngeal-aspirate and stool specimens (128). A study conducted at Texas Children's Hospital found that diagnostic yield is increased when three gastric aspirates are obtained on three consecutive mornings; diagnostic yield was improved by 25% with a second sample and an additional 8% with a third gastric aspirate sample (124).

Bronchial secretions (induced sputum) are obtained by stimulating cough with an aerosol solution of 5% sodium chloride, typically after the child is pretreated with a β-agonist (commonly salbutamol) to prevent bronchospasm, and followed by chest percussion (131, 132). The aerosol is heated in a nebulizer at 46 to 52°C (114.8 to 125.6°F) and administered to the patient for 10 to 15 min. This method gives good results and may be superior to gastric lavage both in yield of positive cultures and in patient acceptance (133). The microbiologic yield from one induced sputum can be equivalent to that from 3 gastric aspirate samples (130). Studies have demonstrated that induced sputum can be obtained safely in a community setting and obtained from children as young as 18 months of age (130, 132, 134).

Bronchial aspirate obtained at bronchoscopy is often thick, and the laboratory processes it using a mucolytic agent, such as *N*-acetyl-L-cysteine. The yield of *M. tuberculosis* from bronchoscopy specimens has been lower in most studies than from properly obtained gastric aspirates or sputum (135, 136). However, bronchoscopic observation of the airways can help establish the likelihood of pulmonary tuberculosis in a child with unknown pulmonary disease (137).

Nucleic Acid Amplification

The original form of nucleic acid amplification studied in children with tuberculosis is the traditional PCR, which uses specific DNA sequences as markers for microorganisms. Various PCR techniques, most using the mycobacterial insertion element IS*6110* as the DNA marker for *M. tuberculosis* complex organisms, have a sensitivity and specificity of more than 90% compared with sputum culture for detecting pulmonary tuberculosis in adults. However, test performance varies even among reference laboratories. The test is relatively expensive, requires fairly sophisticated equipment, and requires scrupulous technique to avoid cross-contamination of specimens.

Use of traditional PCR in childhood tuberculosis has been limited. Compared with a clinical diagnosis of pulmonary tuberculosis in children, sensitivity of PCR has varied from 25 to 83% and specificity has varied from 80 to 100% (138–141). The PCR of gastric aspirates may be positive in a recently infected child even when the chest radiograph is normal, demonstrating the occasional arbitrariness of the distinction between tuberculosis infection and disease in children. The traditional PCR may have a useful but limited role in evaluating children for tuberculosis. A negative PCR never eliminates tuberculosis as a diagnostic possibility, and a positive result does not confirm it. The major use of PCR is evaluating children with significant pulmonary disease when the diagnosis is not established readily by clinical or epidemiologic grounds.

The GeneXpert MTB/RIF assay (Xpert) (Cepheid inc. Sunnyvale, CA) is an automated molecular nucleic acid amplification test that can detect the presence in specimens of *M. tuberculosis* and rifampin resistance within 2 hours (126).The WHO currently recommends use of Xpert for children with suspected pulmonary tuberculosis (87). Multiple meta-analyses evaluating use of Xpert for children have demonstrated improved sensitivity (62 to 98%) compared to that of smear microscopy for the diagnosis of pulmonary tuberculosis (126, 142). However, the yield is lower than for culture, and culture should be performed whenever possible; use of Xpert should not replace culture. One meta-analysis of childhood tuberculosis Xpert studies found that among children with clinically suspected pulmonary tuberculosis, 12% had specimens that were culture positive, whereas 11% had positive specimens by Xpert. Additionally, only 2% of all of the culture-negative children who were started on empiric therapy for suspected pulmonary tuberculosis were Xpert positive (142). A study comparing sensitivity of Xpert on gastric aspirate samples and induced sputum demonstrated similar sensitivities between the two sample types (77.1% and 85.7%, respectively, for smear-positive samples); however, a combination of the two methods allows for improved sensitivity (95.6% for smear-positive samples and 62.5% for smear-negative, culture-positive samples) (143). A meta-analysis evaluating use of Xpert for both adults and children using nonrespiratory samples demonstrated improved sensitivity compared to that of smear microscopy for lymph node samples (pooled sensitivity of 83.1%) and CSF (pooled sensitivity of 80.5%); based on this study, the WHO now recommends use of Xpert for diagnosis of tuberculous lymphadenitis and tuberculous meningitis (87, 144).

MANAGEMENT

The first-line drugs, their formulations, and their pediatric doses are listed in Table 4.

Exposure

Children who have been exposed to potentially infectious adults with pulmonary tuberculosis but are free of symptoms and have a negative physical examination and chest X ray should be started on treatment, usually

TABLE 4 First-line drugs for the treatment of tuberculosis in children

Drug	Dosage form(s)	Daily dose (mg/kg/day)	Twice-wkly dose (mg/kg/dose)	Maximum daily dose
Ethambutol	Tablets: 100 mg, 400 mg	20–25	50	2.5 g
INH[a,b]	Scored tablets: 100 mg, 300 mg Syrup[c]: 10 mg/ml	10–15[b]	20–30	Daily, 300 mg; twice wkly, 900 mg
PZA	Scored tablets: 500 mg	30–40	50	2 g
RIF[a]	Capsules: 150 mg, 300 mg Syrup (formulated in syrup from capsules)	10–20	10–20	Daily, 600 mg; twice wkly, 600 mg

[a]Rifamate is a capsule containing 150 mg of INH and 300 mg of RIF. Two capsules provide the usual adult daily doses of each drug.
[b]When INH is used in combination with RIF, the incidence of hepatotoxicity increases if the INH dose exceeds 10 mg/kg/day.
[c]Most experts advise against the use of INH syrup due to instability and a high rate of gastrointestinal adverse reaction (diarrhea, cramps) when more than 5 ml is given.

INH only, if younger than 5 years of age or if they have other risk factors for the rapid development of tuberculosis disease, such as immunocompromise of some kind (145, 146). Failure to do so may result in development of severe tuberculosis disease even before the TST or IGRA result turns positive; the "incubation period" of disease may be shorter than that for the test of infection. The child is treated for a minimum of 8 to 10 weeks, usually with INH, after contact with the infectious case is broken (by physical separation or effective treatment of the case) and the TST or IGRA is repeated; if the second test is positive, infection is documented and INH should be continued for a total duration of 9 months, but if the second test is negative, the treatment can be stopped. If the exposure was to a case with an INH-resistant but rifampin (RIF)-susceptible isolate, RIF is the recommended treatment.

Two circumstances of exposure deserve special attention. A difficult situation arises when the exposed child may not react to a test of infection because of immunocompromise. These children are particularly vulnerable to rapid progression of tuberculosis, and it will not be possible to tell if infection has occurred. In general, these children should be treated as if they have tuberculosis infection.

The second situation is exposure of a newborn to a mother (or other adult) with a positive TST or, rarely, a nursery worker with contagious tuberculosis. The management is based on further evaluation of the mother (96).

1. The mother has a normal chest radiograph. No separation of the infant and mother is required. Although the mother should receive treatment for tuberculosis infection and other household members should be evaluated for tuberculosis infection or disease, the infant needs no further work-up or treatment unless a case of disease is found.

2. The mother has an abnormal chest radiograph. The mother and child should be separated until the mother has been evaluated thoroughly. If the radiograph, history, physical examination, and analysis of sputum reveal no evidence of active pulmonary tuberculosis in the mother, it is reasonable to assume that the infant is at low risk of infection. However, if the mother remains untreated, she may later develop contagious tuberculosis and expose her infant. Both the mother and infant should receive appropriate follow-up care, but the infant does not need treatment. If the radiograph and clinical history are suggestive of pulmonary tuberculosis in the mother, the child and mother should remain separated until both have begun appropriate chemotherapy. The infant should be evaluated for congenital tuberculosis. The placenta should be examined. If the mother has no risk factors for drug-resistant tuberculosis, the infant should receive INH and close follow-up care. The infant should have a TST at 3 or 4 months after the mother is judged to no longer be contagious; evaluation of the infant at this time follows the guidelines for other exposures of children. If no infection is documented at this time, it would be prudent to repeat the TST in 6 to 12 months. If the mother has tuberculosis caused by a multidrug-resistant isolate of *M. tuberculosis* or she has poor adherence to therapy, the child should remain separated from her until she no longer is contagious or the infant can be given a BCG vaccine and be kept separated until the vaccine "takes" (marked by a reactive TST).

There are insufficient data to determine the optimal management for children exposed to an adult or adolescent with multidrug-resistant (MDR) pulmonary tuberculosis. The current recommendation for children <5 years old and immunocompromised children is treatment with a fluoroquinolone-based regimen with or without either ethambutol or ethionamide for at least 6 months (147).

Infection

The recommendation for treatment of asymptomatic individuals with tuberculosis infection is based on data from several well-controlled studies; it applies particularly to children and adolescents who are at high risk for the development of overt disease but at very low risk for the development of the main toxic manifestation of INH therapy, which is hepatitis (148–151). The large, carefully controlled U.S. Public Health Study of 1955, followed by others, demonstrated the favorable effect of 12 months of INH on the incidence of complications due to progression of tuberculosis infection. The younger the tuberculin reactor, the greater the benefit (152).

The American Thoracic Society and the CDC (153) recommend that INH treatment of tuberculosis infection be given to all positive tuberculin reactors at risk for developing disease. The question arises as to how long the protective effect can be expected to last. Comstock and associates (154), in their final report on INH prophylaxis in Alaska, demonstrated the protective effect of 1 year of treatment to be at least 19 years. Hsu (150) reported on 2,494 children monitored for up to 30 years and showed that adequate drug treatment prevented reactivation of tuberculosis during adolescence and

into young adulthood. It is likely that the decreased risk of tuberculosis after INH therapy may be lifelong in children infected with INH-susceptible tubercle bacilli. Failure of INH therapy after exposure to INH-resistant *M. tuberculosis* has been documented.

The dosage of INH to be used has had little study. Most investigators have used a regimen based on 4 to 8 mg/kg of body weight/day, usually taken all at once, for a period of 6 to 12 months. A dose of 5 mg/kg/day was found to be satisfactory in one study (155). Most clinicians prescribe a dose of 10 to 15 mg/kg/day to a total of 300 mg/day for treatment of infection to be sure of achieving therapeutic levels even among patients who inactivate the drug rapidly by acetylation (156).

A duration of 9 months of INH therapy has been recommended for children in the United States by the AAP and CDC for many years (157), while the WHO recommends a 6-month course for children living in high-burden, low-resource countries. INH is taken daily under self-supervision or can be taken twice weekly as directly observed therapy (DOT) (146). INH treatment of tuberculosis infection is effective when adherence to the regimen is high, but adherence and completion rates are often low (1, 158–160). Several other, shorter regimens have been studied and appear to be as effective as 9 months of INH but with higher completion rates. One alternative regimen is RIF administered daily for 4 months, which can be used in any child but is especially useful when the child is infected with an INH-resistant but RIF-susceptible strain of *M. tuberculosis* (161, 162). Several case-control and observational studies have shown that a 3-month course of INH and RIF is also effective in preventing progression to tuberculosis disease. This regimen has been used for children in several European countries. A newer regimen is the combined use of INH and rifapentine, a rifamycin with a long half-life, administered together once a week for 12 weeks. A large randomized controlled trial with children 2 to 17 years of age with tuberculosis infection compared a regimen of 12 once-weekly doses of combined rifapentine and isoniazid given via DOT with 9 months of self-administered isoniazid monotherapy (163). This study demonstrated high and equivalent efficacies between the two regimens, with equivalent levels of safety and tolerability. The 12-dose regimen, however, is not recommended for children younger than 2 years because of lack of pharmacokinetic data for rifapentine in this age group (164). If the infecting strain is resistant to both INH and RIF, a fluoroquinolone-based regimen with or without addition of a second drug is often used, though there are no clinical trial data to support any specific regimen.

Disease

In 2010 the WHO revised guidelines for treatment of tuberculosis in children. Previous recommendations were extrapolated from adult data, and newer pharmacokinetic studies in children demonstrated lower serum concentration levels in children when using the mg/kg dosing used in adult populations. Further, pharmacokinetic studies using the increased dosing regimens recommended in the revised WHO guidelines demonstrated higher blood levels of antituberculosis drugs than obtained using previous doses without increased toxicity (156, 165, 166).

Clinical trials of antituberculosis drugs in children are difficult to perform, mostly because of the difficulty in obtaining positive cultures at diagnosis or relapse and the need for long-term monitoring (167). Recommendations for treating children with tuberculosis were extrapolated historically from clinical trials of adults with pulmonary tuberculosis. However, during the past 30 years, the results of a large number of clinical trials involving only children have been reported. Patients with only hilar adenopathy can be treated successfully with INH and RIF for 6 months (168). Several major studies of 6-month therapy in children with pulmonary tuberculosis using at least three drugs in the initial phase have been reported (169–172). The most commonly used regimen was 6 months of INH and RIF supplemented during the first 2 months with pyrazinamide (PZA). The overall success rate has been greater than 98%, and the incidence of clinically significant adverse reactions is less than 2%. Using twice-weekly medications (under DOT) during the continuation phase was as effective and safe as daily administration. Several studies used twice-weekly therapy throughout the treatment regimen with excellent success (170, 171), and one used daily therapy for only the first 2 weeks. The 6-month, three-drug regimen was successful, tolerated well, and less expensive than the 9-month regimen. It also effects a cure faster, so there is a greater likelihood of successful treatment if the child becomes nonadherent later in therapy. The WHO recommends using this three-drug regimen for children who live in areas with a low HIV prevalence or who are HIV negative and live in areas with a low prevalence of INH resistance (<4%). However, in order to prevent the development and transmission of MDR tuberculosis, for children living in areas with high rates of HIV infection and/or INH resistance, a 6-month regimen of INH and RIF supplemented with

PZA and ethambutol for the first 2 months is recommended (166). Many experts recommend starting a fourth drug, usually ethambutol, in all suspected cases of childhood pulmonary tuberculosis until it can be determined that the child has tuberculosis susceptible to at least INH and RIF (96, 173, 174).

Controlled treatment trials for various forms of extrapulmonary tuberculosis are rare (175). Several of the 6-month, three-drug trials with children included extrapulmonary cases (170, 176). Most non-life-threatening forms of extrapulmonary tuberculosis respond well to a 6-month regimen including INH, RIF, and PZA. One exception may be bone and joint tuberculosis, which may have a high failure rate when 6-month chemotherapy is used, especially when surgical intervention has not taken place; 9 to 12 months of treatment with four-drug therapy for the first 2 months followed by 10 months of INH and RIF is recommended (177).

Tuberculous meningitis usually is not included in trials of extrapulmonary tuberculosis therapy because of its serious nature and low incidence. Treatment with INH and RIF for 12 months generally is effective (178). A study from Thailand showed that a 6-month regimen including PZA for serious tuberculous meningitis led to fewer deaths and better outcomes than did longer regimens that did not contain PZA (179). Most children are treated initially with four drugs (INH, RIF, PZA, and ethionamide or an injectable drug). The PZA and fourth drug are stopped after 2 months, and INH and RIF are continued for a total of 9 to 12 months. Although there are no clinical trials with children, based on adult observational studies and retrospective studies with children, use of linezolid appears to have some clinical benefit when some of the usual drugs cannot be used due to drug resistance or intolerance (180). Additionally, based on adult studies, use of a fluoroquinolone may lead to improved clinical outcomes (72, 181). Use of corticosteroids reduces the morbidity and mortality of tuberculous meningitis (182). Neurosurgical interventions, usually shunting of CSF, are frequently required when hydrocephalus is present (183). As an alternative, acetazolamide has been used to decrease CSF production and, therefore, intracranial pressure when surgical shunting cannot be performed safely or in a timely manner.

Drug Resistance

MDR *M. tuberculosis* is defined by the resistance of the organism to INH and RIF. Extensively drug-resistant tuberculosis is defined by the resistance of an MDR organism in addition to one of the injectable medications and a fluoroquinolone. Patterns of drug resistance in children tend to mirror those found in adult patients in the population (184–186). Outbreaks of drug-resistant tuberculosis in children occurring at schools have been reported (187). When selecting a medication regimen for the treatment of childhood drug-resistant tuberculosis, decisions should be guided by drug susceptibility testing on the child's isolate, or, if not available, the pattern of resistance from the source case's isolate (188, 189).

Therapy for drug-resistant tuberculosis is successful only when at least two bactericidal drugs to which the infecting strain of *M. tuberculosis* is susceptible are given (190, 191). When INH resistance is considered a possibility, on the basis of epidemiologic risk factors or the identification of an INH-resistant source case isolate, an additional drug, usually ethambutol or streptomycin, should be given initially to the child until the exact susceptibility pattern is determined and a more specific regimen can be designed. Most children with INH-monoresistant tuberculosis respond well to a 6- to 9-month regimen of RIF, PZA, and ethambutol administered daily. Medications used for the treatment of MDR tuberculosis have been placed into 5 groups (Table 5). However, there are limited pediatric formulations and limited pharmacokinetic and safety data for the use of many of these medications in children. When selecting therapy, at least four but ideally five effective medications should be given (188, 189). Exact treatment regimens must be tailored to the specific pattern of drug resistance (192). The duration of therapy usually is extended to at least 9 to 12 months (193). The WHO has recently recommended shorter treatment regimens for children with confirmed RIF-resistant or MDR pulmonary tuberculosis. Although recommendations are based primarily on adult data, the shorter regimens should also be effective in children (194). Surgical resection of a diseased lung or lobe is rarely required in children. An expert in tuberculosis always should be involved in the management of children with drug-resistant tuberculosis infection or disease (195).

There are two new antituberculosis medications: delamanid and bedaquiline. These medications have been approved for use in treatment of MDR-tuberculosis in adults (196, 197). Studies on pharmacokinetics and safety of delamanid in HIV-uninfected children as young as 6 years have demonstrated an excellent safety profile (197–200). There are ongoing studies in younger children. The Sentinel Project recommends use of delamanid in children older than 6 years who weigh more than 20 kg with MDR tuberculosis with additional resistance to second-line agents, those with intolerance to second-

TABLE 5 Drugs used for treatment of MDR tuberculosis in children[a]

Drug group	Drug name	Daily dosage (mg/kg)	Maximum dose (mg)
Group 1: oral first-line drugs	Ethambutol	20–25	2,000
	PZA	30–40	2,000
Group 2: injectable agents	Amikacin	15–20	1,000
	Kanamycin	15–20	1,000
	Capreomycin	15–20	1,000
	Streptomycin	20–40	1,000
Group 3: fluoroquinolones	Ofloxacin	15–20	300
	Levofloxacin	15–20	750
	Moxifloxacin	7.5–10	400
Group 4: second-line oral drugs	Cycloserine (or terizidone)	15–20	1,000
	para-Aminosalicylic acid	150–200	1,000
Group 5: drugs of uncertain value	Linezolid	10 twice daily	600
	Amoxicillin-clavulanate	40 twice daily	4,000
	Clarithromycin	7.5 twice daily	1,000
	Meropenem	20–40	6,000
	Clofazimine	2-3	200

[a]Courtesy of The Sentinel-Project, Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide (189).

line medications, and those with high risk of treatment failure, such as children with HIV infection. Bedaquiline can be used in children 12 years and older with resistance or intolerance to an injectable medication. The recommended treatment duration is 24 weeks for both medications (197, 200).

Adherence and DOT

For many families with a child with tuberculosis, the disease is one of many social and other problems in the family's life, and at certain times, other problems may supersede the perceived importance of tuberculosis (201). To combat this problem of nonadherence with treatment, most health departments have developed programs of DOT in which a third party, usually but not always a health care worker, observes the administration of each dose of medication. DOT should be considered standard therapy for children with tuberculosis disease. The clinician should coordinate this treatment with the local health department. In our clinic, all children with tuberculosis are treated exclusively with DOT, which can be given at an office, clinic, home, school, work, or any other setting and can be observed in person or using video technology. It is highly effective and safe, and the patient satisfaction is high if it is offered as a special service to treat tuberculosis. High-risk children with tuberculosis infection are being treated with DOT at schools or in other locations to ensure completion of therapy. DOT also should be considered for all child contacts of adult tuberculosis patients, especially when the adult also is receiving DOT. Although specific controlled studies are lacking, twice-weekly DOT appears to be effective for treating tuberculosis exposure and infection in children and adolescents.

Follow-Up

Follow-up of children treated with antituberculosis drugs has become more streamlined in recent years. The patient should be seen monthly while receiving chemotherapy, both to encourage regular taking of the prescribed drugs and to check, by a few simple questions (concerning appetite and well-being) and a few observations (weight gain, appearance of skin and sclerae, and palpation of liver, spleen, and lymph nodes), that the disease is not spreading and that toxic effects of the drugs are not appearing. Routine biochemical monitoring for hepatitis is not necessary in children, unless they have liver disease or are taking other hepatotoxic drugs. Repeat chest radiographs should be obtained 1 to 2 months after the onset of chemotherapy to ascertain the maximal extent of disease before chemotherapy takes effect; thereafter, they rarely are necessary. Chemotherapy has been so successful that follow-up beyond its termination is not necessary, except for children with serious disease, such as tuberculous meningitis, or those with extensive residual chest radiographic findings at the end of chemotherapy. Chest radiograph findings resolve slowly; it is typical that enlarged lymph nodes take 2 to 3 years to resolve, well beyond the completion of ultimately successful chemotherapy. A normal chest radiograph is not a criterion for stopping therapy.

PUBLIC HEALTH ASPECTS OF CHILDHOOD TUBERCULOSIS

It is hoped that it has become obvious that the control of tuberculosis in children—for a community and for individuals—depends on close cooperation between the clinician and the local health department (202). It is critically important that clinicians report cases of tuberculosis to the health department as soon as possible (203). Public health law in all U.S. states requires that the suspicion of tuberculosis disease in an adult or child be reported immediately to the health department (204). The clinician should not wait for microbiologic confirmation of the diagnosis because it is this reporting that leads to the initiation of the contact investigation that may find infected children and allow them to be treated before disease occurs (205–207). The child may progress from infection to disease before intervention can occur if the clinician waits for confirmatory laboratory results. The clinician should always feel free to contact the local health department about special issues involving tuberculosis exposure, infection, or disease in a child. Not every clinical situation can be anticipated by normal guidelines, and in some cases, an unusual intervention may be warranted.

It is estimated that about 1 million children in the United States and 67 million children in the world have infection by *M. tuberculosis*. The major purpose of finding and treating these children is to prevent future cases of tuberculosis. Frequent or periodic skin testing of children, however, will prevent few cases of childhood tuberculosis, especially if the screening is centered on school-aged children (who rarely develop primary disease) (208). The major purpose of testing children is to prevent future cases of tuberculosis in adults. The infection rates are low among young children, even in very-high-risk groups in most economically developed nations (209). The best way to prevent childhood tuberculosis is via prompt contact investigation centered on adults with suspected contagious tuberculosis (210). This investigation has a high yield—on average, 30 to 50% of childhood household contacts are infected—but also finds the most important individuals, those most recently infected who are in the period of their lives when they are most likely to develop tuberculosis disease. The most important activity in a community to prevent cases of childhood tuberculosis is the contact investigation activity of the public health department.

If perfect contact investigations were performed and foreign-born children who have migrated were tested for tuberculosis infection, there would be virtually no reason to test any other children because all infected children would be found. Obviously, these two activities do not occur in a perfect fashion, and testing of certain selected individuals is appropriate. The CDC and AAP have changed and refined their recommendations for tuberculin skin testing of children several times in the past decade. The AAP continues to emphasize that routine testing of all children, including school-based programs that include populations at low risk, has a low yield of positive results and a large number of false-positive results, representing an inefficient use of limited health care resources (146). Children without specific risk factors who reside in areas with a low prevalence of tuberculosis, therefore, do not need to have any routine testing for tuberculosis infection. School-based testing may be appropriate only for children with specific risk factors (211). In the United States, a child should be considered at increased risk if the child was born in, has resided in, or has traveled (nontourist) to a country with high tuberculosis rates (Central and South America, Africa, Asia, and Eastern Europe); there is a family history of tuberculosis infection or disease; the child is in foster care; or the child is a member of a group identified locally to be at increased risk for tuberculosis infection (examples may include migrant worker families, the homeless, and certain census tracts or neighborhoods).

Much of the focus on testing should be placed on identification of risk factors for a child being in a group with a high prevalence of infection. Although some risk factors may apply across the country, local health departments must identify those risk factors that are germane to their area. Clinicians and their organizations must work closely with local health departments to establish which children should be tested and which should not. Health departments should advise school districts as to whether any type of school-based testing is appropriate and what nature it should take. Social and political problems can occur when selective testing is suggested. What is correct from a public health point of view may not be easy to translate into a workable and generally acceptable policy. Local clinicians can be extremely helpful to health departments in advancing prudent and reasonable tuberculosis control policies, particularly when other government or public agencies are involved.

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