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From Basic Science
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Chapter 16: Tuberculosis in Children

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16.1. Introduction

The incidence and prevalence of pediatric tuberculosis (TB) worldwide varies significantly according to the burden of the disease in different countries. It has been estimated that 3.1 million children under 15 years of age are infected with TB worldwide. According to the World Health Organization (WHO), children with TB represent 10 % to 20 % of all TB cases. The majority of these cases occur in low-income countries where the prevalence of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) is high. TB occurs frequently among disadvantaged populations, such as malnourished individuals, and those living in crowded areas. According to WHO reports, India, China, Pakistan, the Philippines, Thailand, Indonesia, Bangladesh, and the Democratic Republic of the Congo account for nearly 75 % of all cases of pediatric TB (World Health Organization 2006, Dye 1990). Furthermore, it has also been reported that TB is responsible in Sub-Saharan countries for between 7 % and 16 % of all episodes of acute pneumonia in HIV-infected children, and for approximately one fifth of all deaths in children presenting with acute pneumonia (Chintu 2002, Jeena 2002).

On the other hand, in developed countries such as the United States (US), while an increase in the incidence of TB of approximately 13 % was reported in all ages from 1985-1994, the rate among children younger than 15 years old increased by 33 %. This was mainly attributed to the HIV epidemic, which increased the risk of developing active TB among persons with latent TB infection and HIV co-infection (American Thoracic Society/Centers for Disease Control and Prevention 2001, Taylor 2005). As in adults, TB equally affects children of both genders (males and females), but an increased risk of mortality exists at the extremes of age. Therefore, young children and especially newborns are at a high life risk when they are exposed to a contagious source (Dye 1999). Since most pediatric cases occur due to a rapid progression of a recent infection with a short incubation period, this implies a high rate of recent transmission in the community. Therefore, the infected and ill children in the community are an indirect, useful parameter for assessing the impact of Tuberculosis Control Program activities.

Pulmonary TB in children has a low bacillary load and cavities are also rarely present. Children also lack the forceful cough mechanism seen in adults. Adolescents and older children are important exceptions since their disease closely resembles

that of adults. In these cases, the disease is frequently associated with unfavorable conditions, such as bad nutrition (Correa 1997).

Most risk factors for the acquisition of TB are usually exogenous to the patient. Thus, the likelihood of being infected depends on the environment and characteristics of the index case. However, the development of active disease also depends on the inherent immunologic status of the host (Alcais 2006, Alet 2003).

16.2. Etiology, transmission and pathogenesis

In about 95 % of cases, TB is an airborne disease, transmitted by particles, or droplet nuclei that are expelled when persons who have pulmonary or laryngeal TB sneeze, cough, speak or sing (Feja 1999). When the recipients are persons without previous natural contact with *M. tuberculosis*, the infectious process is denominated primary infection. When this infection evolves to the disease, it is called primary TB (Vallejo 1994).

Droplet nuclei containing between one to 10 bacilli and a diameter close to 10 μm are expelled with the cough, suspended in the air and transported by air currents. Normal air currents can keep them airborne for prolonged periods of time and spread them throughout rooms or building. Some of these droplet nuclei, usually larger than 10 μm , are inhaled and anchored in the upper respiratory tract (Wells 1995). The mucus and the ciliary system of the respiratory tract avoid further progression of mycobacteria.

The effective infective droplet nucleus is very small; measuring 5 μm or less, it is able to avoid the mucus and ciliary system action and produce the anchorage in bronchioles and respiratory alveoli. The small size of the droplets allows them to remain suspended in the air for prolonged periods of time. Although theoretically a single organism may cause disease, it is generally accepted that about five to 200 inhaled bacilli are necessary for a successful infection. After inhalation, the bacilli are usually installed in the midlung zone, into the distal and subpleural respiratory bronchioles or alveoli.

Subsequently, alveolar macrophages phagocytose the inhaled bacilli. However, these first macrophages are unable to kill mycobacteria and the bacilli continue their replication inside these cells. Logarithmic multiplication of the mycobacteria takes place within the macrophage at the primary infection site. Thereafter, transportation of the infected macrophages to the regional lymph nodes occurs leading to the lymphohematogenous dissemination of the mycobacteria to other lymph nodes and organs such as kidneys, epiphyses of long bones, vertebral bodies, jux-

taependymal meninges adjacent to the subarachnoid space, and, occasionally, to the apical posterior areas of the lungs. In addition, chemotactic factors released by the macrophages attract circulating monocytes to the infection site, leading to their differentiation into mature macrophages with increased capacity to ingest and kill free bacteria (Correa 1997, Starke 1996, Vallejo 1994).

Two or three weeks after the initial *M. tuberculosis* infection, a cell-mediated immune response is fully established. While CD4+ T helper cells activate the macrophages to kill the intracellular bacteria and finally cause epithelioid granuloma formation, CD8+ suppressor T cells lyse the infected macrophages, resulting in the formation of caseous granulomas with central necrosis. Due to the fact that mycobacteria are not able to grow under the adverse conditions of the extracellular environment, most infections are controlled by the host immune system. The only evidence of a real and effective infection is a positive TST (Correa 1997, Seibert 1932, Seibert 1934). However, the initial pulmonary infection site, which is denominated “primary complex or Ghon focus” and its adjacent lymph nodes, sometimes reach sufficient size to develop necrosis and calcification demonstrable by radiographs (Feja 2005, Schluger 1994).

As in adults, childhood TB is mostly due to *M. tuberculosis*. The proportion of both pediatric and adults TB cases caused by *M. bovis* is very low. It is generally associated with close contact with cattle, and is variable from one country to another and even from region to region inside the same country (see Chapter 8).

Bacille Calmette-Guérin (BCG) vaccination applied to newborns reproduces a natural infection under controlled conditions in an attempt to avoid a first productive contact - leading to a severe disease - between children and virulent *M. tuberculosis* strains spread in the community. During further contacts with *M. tuberculosis* from a natural infectious source, a child’s immune system, already prepared by BCG vaccination, will be more capable of controlling this new infection. BCG vaccination can sometimes cause a disease clinically indistinguishable from TB, but this usually occurs in patients with severe impairment of their immune system (Jacobs 1993, Vallejo 1994, see Chapters 8 and 10).

16.2.1. Infection acquisition

Most pediatric TB cases can be traced to a household relative contact. In general, it is believed that the younger the child with a positive tuberculin skin test (TST), the higher the probability of an infectious source within the home. This situation occurs when repetitive or constant contact with the infectious source - generally fam-

ily members - takes place. Therefore, when a child is diagnosed, a search should be performed for an adult case with a high bacillary load in the respiratory tract (Alet 1986). On the other hand, older children may become infected from an external source, such as schoolmates, team leaders or young adults outside the home.

The presence of extensive pulmonary lesions, such as cavities, is the most important individual human factor in determining the infectious power, since these lesions are associated not only with an important concentration of oxygen that allows active bacillary multiplication, but also with a rapid pathway to the external environment. The amount of bacilli released into the atmosphere under these conditions is enough to produce the transmission from person to person (Correa 1997, Schluger 1994).

The degree of pulmonary involvement is another important factor, since the extension of the lesions is related to the bacillary load, the intensity and frequency of coughing, and the number of cavities that may propagate these bacilli. Rarely, non-pulmonary localization of the disease with high infectious power, such as the laryngeal form, becomes an infectious source. In this case, simple actions such as talking can cause the elimination of an important amount of mycobacteria (Correa 1997).

Socioeconomic factors as well as the overcrowded living places in urban areas increase the risk of infection allowing larger contacts with infected persons. Race may not be considered an independent risk factor (Brailey 1996).

The infectious capacity of the source case is also associated with the virulence of the bacilli.

Environmental factors also contribute to the likelihood of acquiring the infection. The concentration of bacilli depends on ventilation of the surroundings and exposure to ultraviolet light. Thus, overcrowding, congregation in schools, poor housing and inadequate ventilation predispose individuals to infection and development of TB (American Academy of Pediatrics 2003).

16.2.2. Infection development

Defects in the level of immunocompetence, especially in cell-mediated immunity, such as HIV infection, are major determinants for development of TB. In general, TB case rates for persons who are co-infected with HIV and *M. tuberculosis* exceed the lifetime risk of persons without HIV co-infection. It has been estimated that for

patients with HIV infection, the risk of developing TB is 7 % to 10 % per year (American Thoracic Society 2000, see Chapter 17).

Children under steroid therapy, cancer chemotherapy, and hematological malignancies have an increased risk of developing TB. Something similar happens with malnutrition, which interferes with cell-mediated immune response and therefore accounts for much of the increased frequency of TB in impoverished patients.

Other infections, such as measles, varicella, and pertussis, may activate quiescent bacilli with subsequent TB development. Individuals with certain human leukocyte antigen types and hereditary factors, including the presence of a *bcg* gene, seem to have a predisposition for TB acquisition (American Thoracic Society 2000, Caminero 2003, see Chapter 6).

In pediatric TB, it is possible to clearly distinguish among three basic stages: exposure, infection, and disease. From a public health point of view, these stages have absolutely different transmission implications and epidemiologic consequences.

Exposure is related to the fact that the child has been in contact with adolescents or adults with suspected or confirmed contagious pulmonary TB. Household is the most frequent setting for exposure although several places that allow a close contact with potentially contagious adults such as school, day care centers and other environments become occasional exposure places. During the 18th century, the “familial hypothesis” raised by the occurrence of familial clustering, dominated medical thinking. However, it was not until the '30s that rigorous epidemiological studies provided solid evidence for the contribution of genetic factors in addition to exposure in the development of TB (Alcais 2006).

In populations that do not include BCG vaccination as part of the infant vaccination scheme, the TST is negative during the exposure period, the chest radiograph is normal, and there are neither signs nor symptoms of disease (World Health Organization 1982). Since a positive TST may take up to three or four months to develop from the time of infection, it is not possible to be precise about whether the child is truly infected during this period.

The hallmark of TB infection is a reactive TST in the absence of signs or symptoms of the disease, and in the presence of a chest radiograph that could be either normal or showing only a granuloma-compatible image (Correa 1997, Starke 1993).

Infection is then clinically different from disease. Disease is the presence of signs and symptoms or radiographic abnormalities after the infection. In adults, the distinction between infection and disease becomes less difficult because the latter may

be the result of dormant bacilli acquired during a past infection. In children, the distinction may not be so clear because the disease more often progresses from an initial or primary infection. From a practical point of view, adults with TB almost always manifest significant radiographic abnormalities and/or clinical symptoms, whereas up to 50 % of pediatric patients may remain asymptomatic with subtle abnormalities on the chest radiograph. Sometimes, erythema nodosum may be the only clinical finding in a child recently infected with *M. tuberculosis* (Jacobs 1993, Centers for Disease Control and Prevention 1999).

16.3. Primary pulmonary tuberculosis

Unfortunately, children younger than five years old may develop disseminated TB in the form of miliary disease or tuberculous meningoencephalitis before the TST result becomes positive. Thus, a very high index of suspicion must be adopted when pediatric patients have a contact history. Children with asymptomatic infection usually have a positive TST result but do not have any clinical or radiographic manifestations. These children may be identified on a routine medical examination, as children who have recently emigrated from a high prevalence country, or adopted children, or they may be identified subsequent to TB diagnosis in household or other contacts (Centers for Disease Control and Prevention 1999, Saltik 1991).

Pulmonary TB in children can range from an asymptomatic primary infection to a progressive primary TB. Primary TB is very often characterized by the absence of signs on clinical evaluation. Asymptomatic presentations are more common among school-age children (80-90 %) than in infants less than one year old (40-50 %) (Correa 1997, Vallejo 1996).

Disease should be suspected if the child has been exposed to a contagious source and if the TST is positive. In contrast to pulmonary TB in adults, the TST following standard procedures is an important element for TB diagnosis in children. Sometimes these patients are identified by a positive TST that may be associated with allergic manifestations such as erythema nodosum and phlyctenular conjunctivitis. Erythema nodosum is a toxic allergic erythema with nodular lesions in the skin or under it, 2 to 3 cm large. These lesions are spontaneously painful and very painful under pressure, and are usually located bilaterally in feet and legs. The erythema nodosum is usually accompanied by pharyngitis, fever and joint inflammation and is more frequent in girls over six years. Phlyctenular conjunctivitis is an allergic keratoconjunctivitis characterized by the presence of small vesicles that usually evolve to ulcers and resolve without scars. The more frequent symptoms

associated to the phlyctenular conjunctivitis are photophobia and an excessive lacrimation (Peroncini 1977).

Progression of the primary infectious complex may lead to enlargement of hilar and mediastinal lymph nodes with resultant bronchial collapse. Progressive primary TB, which is considered to be a serious form of the disease, may develop when the primary focus cavitates and bacteria spread through contiguous bronchi. Lympho-hematogenous dissemination, especially in young patients, may lead to miliary TB when caseous material reaches the bloodstream from a primary focus or a caseating metastatic focus in the wall of a pulmonary vein (Weigert focus). Tubercular meningoencephalitis may also result from hematogenous dissemination (Newton 1994, Smith 1992).

When the disease is controlled by the host immune system, those bacilli spread by the bloodstream may remain dormant in all areas of the lung or other organs for several months or years. Afterwards, in adult life, a progression to the disease may occur from an endogenous reactivation. Primary TB includes various presentations of the disease as described in the following sections.

16.3.1. Endobronchial tuberculosis

This form of pulmonary TB occurs when the infected lymph nodes erode into a bronchus. Enlargement of lymph nodes may result in signs suggestive of bronchial obstruction or hemidiaphragmatic paralysis. Dysphagia due to esophageal compression may be observed. Vocal cord paralysis may also occur as a result of local nerve compression.

A partial or complete bronchial obstruction can also occur. Usually it is the result of deposition of caseous material within the lumen. Obstructive hyperaeration of a lobar segment or a complete lobe is less common in pediatric patients while cavities, bronchiectasis and bullous emphysema are occasionally seen. Even in the presence of extensive pulmonary disease, many older children are asymptomatic at the time of diagnosis. In general, however, children are more likely to present with wheezing, cough, fever, and anorexia as part of the symptoms (Lincoln 1958, Starke 1996, Vallejo 1995).

Persistent cough may be indicative of bronchial obstruction, while difficulty in swallowing may result from esophageal compression. Hoarseness or difficult breathing may suggest vocal cord paralysis.

16.3.2. Progressive primary pulmonary tuberculosis

Progression of the pulmonary parenchymal component leads to enlargement of the caseous area and may lead to pneumonia, atelectasis, and air trapping. This is more likely to occur in young children than in adolescents. The child usually appears ill with symptoms of fever, cough, malaise, and weight loss.

This form presents classic signs of pneumonia, including tachypnea, dullness to percussion, nasal flaring, grunting, egophony, decreased breath sounds, and crackles.

16.3.3. Pleural involvement

Pleural effusion due to TB usually occurs in older children and is rarely associated with miliary disease. Typical history reveals an acute onset of fever, chest pain that increases in intensity on deep inspiration, and shortness of breath. The pain accompanies the onset of the pleural effusion, but after that the pleural involvement is painless. Fever usually persists for 14-21 days.

The signs of pleural effusion include tachypnea, respiratory distress, decreased breath sounds, dullness to percussion, and occasionally, features of mediastinal shift.

16.3.4. Reactivated pulmonary disease

Chronic pulmonary or adult-type TB is rare in children. This condition generally occurs in children who are at least seven years old when they develop TB, but is more common in older children and adolescents. Usually, it has a subacute presentation with weight loss, fever, cough, and, rarely, hemoptysis.

When the primary infection has not been treated properly, the lesion can reactivate from dormant bacilli in either lymph nodes or parenchymal nodules. In contrast to primary disease, the characteristic feature of reactivation is the parenchymal involvement, which usually evolves to cavities or diffuse infiltrates, without significant radiograph changes in pulmonary adenopathies (Peroncini 1979).

Physical examination may show no abnormalities or may reveal posttussive crackles.

16.3.5. Primary tuberculosis complications

TB complications are dependent on the delay in diagnosis and start of treatment.

Miliary disease and tubercular meningoencephalitis are the earliest and most deadly complications of primary TB. Pulmonary complications of TB include the development of pleural effusions and pneumothorax. Complete obstruction of a bronchus can result if caseous material extrudes into the lumen. Bronchiectasis, stenosis of the airways, bronchoesophageal fistula, and endobronchial disease caused by penetration through an airway wall are other complications that may occur in primary TB. When dissemination of the disease occurs, perforation of the small bowel, obstruction, enterocutaneous fistula, and the development of severe malabsorption may complicate TB of the small intestine.

Pericardial effusion can be an acute complication or can resemble chronic constrictive pericarditis. Renal complications, including hydronephrosis and autonephrectomy usually do not occur in children. Paraplegia may arise as a complication of TB located in the spine (i.e. tubercular spondylitis) (American Academy of Pediatrics 2003, Correa 1997, Jacobs 1993, Lincoln 1958).

16.4. Non-respiratory disease

Non-respiratory disease implies the dissemination of the bacilli through the circulatory and lymphatic systems. Localizations other than pulmonary are more frequent in children than in adults. Extrapulmonary TB includes peripheral lymphadenopathy, miliary TB, tubercular meningitis, skeletal TB, and other organ involvement (Caminero 2003, American Academy of Pediatrics 2003, American Thoracic Society 2000).

16.4.1. Peripheral lymphadenopathy

In fact, the high tropism that *M. tuberculosis* shows to lymph nodes in children under five years old is remarkable. In the majority of these cases, the localization is intrathoracic affecting mainly the mediastinal lymph nodes. Close to 25-35 % of these forms have extrathoracic localizations, such as on the neck lymph nodes called scrofula. However, it is important to remark that when scrofula affects children under five years old, it is caused by non-tuberculous mycobacteria (NTM) in 75 % to 80 % of cases. In different geographic areas, the prevalence of NTM varies greatly, being more prevalent in hot climate regions. It has been estimated that 65 % to 80 % of children under 12 years old may be infected with *Mycobacterium*

avium complex; 10 % to 20 % with *Mycobacterium scrofulaceum*; and 10 % with *M. tuberculosis*. In contrast, more than 90 % of culture-proven mycobacterial lymphadenitis in adults and children older than 12 years are caused by *M. tuberculosis* (Johnson 1998, Saltik 1991).

Although in developed countries the scrofula presentation is mostly caused by *M. avium* and *M. scrofulaceum*, the real situation in low-income countries still remains to be elucidated. To distinguish between NTM and *M. tuberculosis* infected lymph nodes is frequently difficult; therefore, surgical dissection and culture of the biopsy material is usually necessary for both diagnostic and therapeutic reasons (Smith 1992, Starke 1995).

Patients with scrofula may complain of enlarged nodes. Fever, weight loss, fatigue, and malaise are usually absent or minimal. Lymph node involvement typically occurs between six to nine months following the initial infection. Lymphadenopathy usually involves the anterior or posterior cervical and supraclavicular nodes. Less commonly involved are the submandibular, submental, axillary, and inguinal lymph nodes. The infected lymph nodes are typically firm, non-tender, and painless, with non-erythematous overlying skin. The nodes are initially non-fluctuant. Lymph node suppuration and spontaneous drainage may occur after caseation and necrosis development (Freixinet 1995, Starke 1995).

16.4.2. Miliary tuberculosis

As was mentioned before, miliary TB can be a complication of primary TB in young children. A rapid onset of fever and associated symptoms may be observed. When the lungs are involved, respiratory signs may evolve to include tachypnea, cyanosis, and respiratory distress, so miliary TB should be considered in a child with a history of cough and respiratory distress.

Miliary TB can also develop from an extrapulmonary form, leading to a disease in two or more organs, usually the brain and liver. Infants are particularly prone to the bacilli spreading throughout their body and development of the miliary form of the disease. Both pulmonary and extrapulmonary miliary forms are particularly severe diseases (Correa 1997, Rodrigues 1993).

16.4.3. Tuberculous meningitis

This is one of the most dangerous complications of TB. Between 30 % and 50 % of children with miliary TB have meningitis at the time of diagnosis. It occurs in up to

5 % to 10 % of cases of TB in children younger than two years old. Thereafter, the frequency drops to less than 1 %.

Because of the frequent insidious onset of the disease, a very high index of suspicion is required to make a timely diagnosis. A subacute presentation can also occur within three to six months after the initial infection. The clinical presentation comprises a variety of signs and symptoms with an insidious or acute start. The signs and symptoms include low-grade persistent fever, malaise, anorexia, weight loss, fatigue, hepatomegaly, splenomegaly and generalized lymphadenopathy, alteration in consciousness and sensorium, stupor and the emergence of focal neurological signs.

As the disease progresses, a deterioration of mental status is accompanied by headache and neck stiffness, photophobia, seizures, coma, and death may occur if a proper diagnosis and early intervention are not promptly started.

Typical cerebrospinal fluid findings include a moderate lymphocytic pleocytosis, low glucose level and an elevated protein concentration. Hyponatremia caused by inappropriate excretion of antidiuretic hormone is frequently seen. Abnormal chest radiographs are seen in 50 % of children with meningitis, but TST can be negative in 40 % of children at the time of diagnosis.

Three stages of tubercular meningitis have been identified:

- in the first stage, no focal or generalized neurological signs are present. Possibly, only nonspecific behavioral abnormalities are found.
- the second stage is characterized by the presence of nuchal rigidity, altered deep tendon reflexes, lethargy, and/or cranial nerve palsies. TB meningitis most often affects the sixth cranial nerve, resulting in lateral rectus palsy. This is due to the pressure of the thick basilar inflammatory exudates on the cranial nerves or to hydrocephalus. The third, fourth, and seventh cranial nerves may also be affected. Fundoscopic changes may include papilledema and the presence of choroid tubercles, which should be carefully sought.
- the final stage comprises major neurological defects, including coma, seizures, and abnormal movements (e.g. choreoathetosis, paresis, paralysis of one or more extremities).

In the terminal phase, decerebrated or decorticated posturing, opisthotonus, and death may occur.

Patients with tuberculomas or tubercular brain abscesses may present with focal neurological signs. Spinal cord disease may result in the acute development of spinal block or a transverse myelitis-like syndrome. A slowly ascending paralysis may develop over several months to years (Correa 1997, Vallejo 1994).

16.4.4. Skeletal tuberculosis

Osteoarticular TB complications appear in 1 % to 6 % of untreated primary infections. Clinical and radiographic presentations vary widely and depend upon the stage of the disease at the time of diagnosis. Skeletal TB may remain unrecognized for months to years because of its lack of specific signs and symptoms and indolent nature.

Bone or joint TB may present acutely or subacutely. Sites commonly involved are the large weight-bearing bones or joints including the vertebrae (50 %), hips (15 %), and knees (15 %). Less common skeletal sites are the femur, tibia, and fibula. Destruction of the bones with deformity is a late sign of TB. Manifestations may include angulation of the spine or “gibbus deformity” and/or the severe kyphosis with destruction of the vertebral bodies or “Pott’s disease”.

Cervical spine involvement may result in atlantoaxial subluxation, which may lead to paraplegia or quadriplegia. TB of the skeletal system may also lead to involvement of the inguinal, epitrochlear, or axillary lymph nodes. (Correa 1997, Vallejo 1995).

16.5. Congenital tuberculosis

Congenital TB is considered a rare event in the whole spectrum of TB presentations. This infection is caused by lymphohematogenous spread during pregnancy from an infected placenta or aspiration of contaminated amniotic fluid.

Symptoms typically develop during the second or third week of life and include poor feeding, poor weight gain, cough, lethargy, and irritability. Other symptoms include fever, ear discharge, and skin lesions, failure to thrive, icterus, hepatosplenomegaly, tachypnea, and lymphadenopathy. Congenital TB diagnosis is based on clinical features and the infant should have at least one of the following proven TB lesions (Correa 1997, Cantwell 1994):

- skin lesions during the first week of life, including papular lesions or petechiae, necrotic or purpuric lesions
- choroidal tubercles in the retina
- documentation of TB infection of the placenta or the maternal genital tract
- presence of a primary hepatic complex (liver and regional lymph-node involvement)
- exclusion of the possibility of postnatal transmission

16.6. Diagnosis

16.6.1. Clinical disease evaluation

Pediatric patients with pneumonia, pleural effusion, or a cavitary or mass lesion in the lung that does not improve with standard antibacterial therapy should be evaluated for TB. This evaluation is also indicated for children with fever of unknown origin, failure to thrive, significant weight loss (more than 10 % of normal weight), or unexplained lymphadenopathy. An adequate clinical history should look for household or adult infectious cases, immigration from high prevalence countries, living in shelters or other risk factors (American Academy of Pediatrics 2003, American Thoracic Society 2000, American Thoracic Society /Centers for Disease Control and Prevention 2001, Correa 1997, Feja 2005, Jacobs 1993, Taylor 2005, Vallejo 1994).

16.6.2. Diagnostic laboratory tests in pediatric tuberculosis

The cornerstone of the diagnosis of pulmonary TB in adults is based on the demonstration of *M. tuberculosis* by means of microbiological and/or molecular methods. Pediatric TB is usually considered a paucibacillary disease, which makes bacteriological diagnosis of TB extremely challenging because of the difficulty in isolating *M. tuberculosis* from clinical specimens. This difficulty decreases as the age of the child increases. Therefore, all tools available in laboratories must be used to diagnose pediatric cases, especially in the very young.

Despite innovations in rapid diagnosis, many of the classic diagnostic tools continue to be useful in the evaluation of TB patients (Caminero 2003).

Specimen collection

The first step in detecting and isolating mycobacteria is to obtain appropriate specimens for bacteriological examination. These specimens are: sputum, gastric lavage, bronchoalveolar lavage, lung tissue, lymph node tissue, pleural fluid, bone marrow, blood, liver, cerebrospinal fluid, urine, and stool, depending on the location of the disease.

Children under 12 years old are rarely able to produce sputum and voluntarily expectorate, and therefore gastric lavage is often used to obtain a specimen in very young children (< 6 years old). The rationale for this presumes that the child has coughed up and swallowed their bronchial secretions. The use of the correct technique for obtaining the gastric lavage is important because of the scarcity of bacilli in children compared to adults. The technique requires a nasogastric tube inserted in an inpatient setting, because the sensitivity of outpatient gastric lavages has not been evaluated. Early morning samples, optimally from three consecutive days, should be obtained before the child has had a chance to eat or move, as these activities dilute the bronchial secretions accumulated during the night. Initially, the stomach contents should be aspirated, and then a small amount of sterile water injected through the nasogastric tube. This aspirate also should be added to the specimen. Since gastric acidity is poorly tolerated by the tubercle bacilli, neutralization of the specimen with 10 % sodium carbonate or 40 % anhydrous sodium phosphate should be performed immediately. Even under the best technical conditions, tubercle bacilli can be only recovered in 70 % of infants and in 30 % to 40 % of ill children.

Sputum specimens may be used in older children who are able to expectorate. Clear instructions for collecting the sputum sample must be given in order to avoid obtaining nasopharyngeal secretions and saliva, which are not acceptable for analysis. More recently, the use of induced sputum, obtained after nebulization with a hypertonic NaCl solution to provoke a productive cough, has been proposed, as it produces high yield results similar to those obtained in adults (SAP 2002). Another technique to obtain bronchial secretions is by stimulating cough using an aerosol solution of propylene glycol in 10 % sodium chloride, or by bronchoalveolar lavage. The bronchoalveolar lavage (instilling a total of 180 mL of saline solution and obtaining the sample by aspiration of the bronchial contents) is an invasive technique and requires the use of anesthesia, so its use in children must be well justified. Besides, bronchoscopy yield has been lower than properly obtained gastric lavages and its role remains controversial in evaluating pulmonary TB.

Bronchoscopy may be useful in determining endobronchial involvement and also in distinguishing *M. tuberculosis* from other opportunistic mycobacterial infections in immunocompromised patients (Abadco 1992, Alet 1986, American Academy of Pediatrics 2003, American Thoracic Society 2000, Newton 1994, Saltik 1991, Smith 1992).

Renal disease is a rare event in children, but when it is suspected, overnight urine specimens must be collected in the early morning and immediately sent for analysis, as the tubercle bacilli poorly tolerate the acid pH of urine.

Other body fluids (e.g. cerebrospinal, pleural, or peritoneal) must be centrifuged and the sediment used to prepare smears to evaluate the presence of acid-fast bacilli (AFB). Smears of cerebrospinal fluid are positive in fewer than 10 % of patients with TB meningitis. Enhancement of the yield may be possible by staining any typical clot (bride veil) formed in cerebrospinal fluid specimens. Increased yield may also be obtained from cisternal or ventricular fluid (Newton 1994, Starke 2000).

Bacteriological techniques

Finding AFB on a stained sputum smear provides a strong preliminary confirmation of TB diagnosis, especially in low-income countries where it has a high positive predictive value for TB (> 98 %). Staining can also give a quantitative assessment of the number of bacilli being excreted. Nevertheless, in children in whom bacilli in the respiratory secretions are sparse, results may be negative. In these cases, a single organism on a slide is highly suggestive and warrants further investigation.

Culture of *M. tuberculosis* is the definitive method to diagnose the disease and must be performed whenever possible in pediatric cases, because it is more sensitive than microscopic examination, and also allows species confirmation and drug susceptibility testing. Conventional cultures on Löwenstein-Jensen solid medium are commonly used in low-income countries, while automated culture methods are widely employed in high-income countries for the rapid detection and recovery of mycobacteria (Caminero 2003) (see Chapters 12 and 14).

Specimens from body sites naturally contaminated, such as sputum and urine, require a decontamination process prior to culture in order to allow the growth of mycobacteria in the culture media, without overgrowth of the commensal flora.

The culture isolation rate from body fluids in children with extrapulmonary TB is usually lower than 50 % (Correa 1997), and it is estimated that only 10 % to 20 % of all pediatric forms can be diagnosed by culture.

Molecular methods

Nucleic acid amplification methods, such as the polymerase chain reaction (PCR), have shown sensitivity and specificity greater than 90 % for detecting smear-positive pulmonary TB in adults. Although the use of this technique in children has not yet been extensively evaluated, several studies have reported sensitivity ranging from 25 % to 83 % in children with pulmonary TB (American Thoracic Society 2000). According to several reports, the sensitivity and specificity of the nucleic acid amplification methods in smear-positive cases may exceed 95 %, but the sensitivity in smear-negative cases, which includes most of the pediatric cases, varies from 40 % to 70 % (Eisenach 1990, Morcillo 2001, Saltini 1998).

To distinguish TB infection from disease has been particularly difficult with the currently available in-house and commercial nucleic acid amplification tests. Specificity is even more controversial, and false positive results have been observed in up to 20 % of controls (Smith 1996).

16.6.3. Tuberculin skin testing

The American Academy of Pediatrics has issued the following guidelines for pediatric testing (American Academy of Pediatrics 2003):

- TST is indicated in children who have been in contact with persons with active TB
- TST is indicated in immigrants from regions in which TB is endemic (e.g. Asia, the Middle East, Africa, Latin America) or children with travel histories to these regions
- TST is indicated in children with radiographic or clinical findings suggestive of TB (Arnadottir 1996, Guvenc 1993)
- Annual TST is indicated in children who are infected with HIV or those living in a household with persons infected with HIV; also in incarcerated adolescents
- Testing at two- to three-year intervals is indicated if the child has been exposed to high-risk individuals, including those who are homeless, adults who are infected with HIV, drug users, residents of nursing homes, and incarcerated adolescents or adults
- Testing in children 4-6 years old and 11-16 years old living in high-prevalence areas is indicated irrespective of the presence of risk factors

Performing an initial TST before the initiation of immunosuppressive therapy is recommended in any patient. TST application should follow the principles defined in the following paragraphs.

Mantoux technique

In the accepted protocol (see Chapter 13) for TST by the Mantoux technique, a standardized antigen preparation containing two tuberculin units of purified protein derivative (PPD) should be injected intradermally into the volar aspect of the forearm using a 27-gauge needle. The test should read by skilled personnel 48-72 hours after administration. The size of induration and not erythema must be measured by placing the ruler transversally to the long axis of the forearm (ruler-based reading).

The Mantoux test is the only skin test acceptable in children evaluation. Multiple puncture techniques should no longer be used because of its intrinsic limitations and inaccuracy (Arnadottir 1996, International Union Against Tuberculosis and Lung Disease 1991, World Health Organization 1963).

Interpretation of tuberculin skin test results

The US Centers for Disease Control and Prevention, and the American Academy of Pediatrics have made recommendations on the size of TST induration that is considered to be a positive result and indicative of disease in different groups of children (Table 16-1). The TST reactivity is interpreted on the basis of a ruler showing 5, 10, and 15 mm. divisions.

For children that have been exposed to highly contagious TB patients, a reaction equal or greater than 5 mm diameter is classified as positive. For other high-risk groups, such as children with increased environmental exposure, or those younger than four years old, a reaction equal or greater than 10 mm is a positive result. For children over 4 years of age who are not at risk of TB, a reaction equal or greater than 15 mm is a positive result (Centers for Disease Control and Prevention 2000, Centers for Disease Control and Prevention 1999).

TST false-positive reactions are often attributed to asymptomatic infection by environmental non-tuberculous mycobacteria (NTM) due to cross-reactivity. False-negative results may be caused by recent vaccination with live-attenuated virus, energy, immunosuppression, immune deficiency, or malnutrition (Flament 1994). Other factors that may cause a false-negative result include improper administration (e.g. subcutaneous injection, injection of too little antigen), improper storage of the PPD material, and contamination. PPD has been recognized to have an initial false-negative rate of 29 % (Batra 2000).

BCG vaccination is used in all developing countries, and is not a contraindication for the TST, but differentiating tuberculin reactions caused by BCG vaccination from those attributable to *M. tuberculosis* infection is sometimes difficult. A history of contact with a person with contagious TB or emigration from a high prevalence country increases the likelihood that a TST induration of 10 mm or more is due to a true infection with *M. tuberculosis*. The reactivity caused by BCG vaccination, which is usually less than 10 mm, generally wanes with time, but multiple BCG vaccinations can perhaps cause a positive TST.

Table 16-1. Tuberculin skin test: cutoff size of reactive area for positive tuberculin reaction

Cut off area (mm)		
≥ 5 mm	≥ 10 mm	≥ 15 mm
Contact to infectious cases with or without symptoms.	Children from high prevalence countries.	Children ≥ 5 years without risk factors
Abnormal chest radiograph consistent with TB.	Residents of shelters and institutions.	
HIV co-infected and other immunosuppression.	Close contact with high-risk adults or adolescents.	
Previous TB.	At a higher risk of TB dissemination. Immunocompromised patients (lymphoma, Hodgkin disease, diabetes mellitus, malnutrition)	
Clinical evidence of active TB	Children < 5 years of age	

The tuberculin reactivity may be boosted after several Mantoux administrations (Guvenc 1993), and may even lead to false positive reactions, and routine annual TST in children is not used in developed countries. Cost-benefit analyses have shown that universal school-based skin testing programs are not effective in finding ill children, and the targeted screening of high risk children is more efficient and less costly than screening all students.

Children showing significant reactions to TST (≥ 10 mm) should have a thorough physical examination, a chest radiograph, and an exhaustive review of contacts for possible exposure to adults with TB or environments with a high risk for TB exposure.

When TB is discovered in a child, it is crucial to search for an infectious source, which should be properly identified, diagnosed and treated. Bacteriological diagnosis and drug susceptibility testing of the mycobacterium causing the disease in the index case is extremely important. It is often impossible to obtain a sputum from young children, so analyzing the strain isolated from the index adult case may be the only way to determine the appropriate treatment for the child (Chadna 2003, Comstock 1974, International Union Against Tuberculosis and Lung Disease 1991, Jacobs 1993).

16.6.4. Imaging Studies

Chest X-ray is a classic diagnostic tool when evaluating patients for pulmonary TB.

Radiographic manifestations

Lymphadenopathy involving the hilar and paratracheal lymph nodes is the hallmark of primary TB in children. Nevertheless, the hilar region may be difficult to evaluate by a posteroanterior radiograph view, so the systematic inclusion of a lateral view radiograph is necessary. When one or several granulomas or calcifications are detected in the lung parenchyma or hilar/mediastinal lymph nodes (primary bipolar complex), these could just be evidence of a past infection with *M. tuberculosis* and do not necessarily indicate active disease. However, the absence of calcification in the lesions lends support to the possibility of active primary disease.

A fan-shaped lesion on the radiograph is a manifestation of bronchial obstruction, leading to segmental disease characterized by atelectasis and consolidation of the involved area. Other chest radiographic observations include linear, interstitial and nodular densities, cavities with consolidation, empyema, bronchiectasis or focal masses.

Meningitis mainly affects the base of the brain. Computed tomography imaging can reveal basal cistern inflammation, hydrocephalus and meningeal enhancement, as well as focal parenchymal abnormalities, such as tuberculomas and infarction.

The radiographic findings in skeletal TB often include irregular areas of destruction, sclerosis, osteopenia, minimal periosteal reaction and slow enlargement of the focus. In adults, tuberculous osteomyelitis usually originates in the epiphysis of long bones with spread into the adjacent joint space. Instead, in children, TB typically affects the metaphysis and can intrude into the growth plate.

Other imaging tools

Computerized tomography scans and magnetic resonance imaging are other valuable tools for the diagnosis of respiratory and non-respiratory TB. In patients with pulmonary TB, these imaging studies can help demonstrate hilar lymphadenopathy, endobronchial TB, pericardial invasion, and early cavitations or bronchiectasis. However, computed tomography scans and magnetic resonance imaging are superfluous when chest radiograph findings are diagnostic.

16.7. Pediatric tuberculosis treatment

Children of five years old or younger, with proven exposure to an active case of pulmonary TB, should immediately begin treatment regardless of the TST or chest X-ray findings. The decision to empirically treat exposed older children is more controversial. There are several aspects of treatment that are markedly different in children and require special consideration, such as the availability of pediatric formulations, dosing, side effects, and follow-up (Correa 1997, Blumberg 2004).

16.7.1. Treatment of asymptomatic tuberculosis infection

The purpose of treating asymptomatic infection is to prevent the development of active disease in the future. This treatment has also been called preventive therapy, chemoprophylaxis or latent TB treatment. The decision to treat children in the different stages of TB - exposure, infection and disease - is based on the risk-benefit ratio and the side effects of the treatment. Since infected children are at a high risk of developing active disease, all infected children should receive preventive chemotherapy (Miller 1993, Starke 1995).

The risk of acquisition of TB is particularly high in very young children (< 5 years old) and in adolescents. Thus, patients in these age groups with a positive TST and no other manifestations should receive prophylactic INH therapy, but active TB must be carefully excluded prior to the initiation of preventive therapy (American Thoracic Society 1994, Comstock 1967, World Health Organization 2001).

Guidelines for the application of preventive chemotherapy vary among countries and even communities in relation to the age of the infected children (Arnadottir 1996, International Union Against Tuberculosis and Lung Disease 1991). But, in spite of age considerations, there is a general consensus about using isoniazid (INH) when the contagious source is a patient with a fully drug-susceptible TB strain (Pape 1993, Rieder 1999). It is extremely important to exclude active disease in order to avoid mycobacteria selection under drug pressure due to a chemo-

therapy based on INH alone, with the consequent development of INH-resistance (Alet 1986, Miller 1993).

In the US, before the advent of latent TB chemotherapy, the reported mortality rates for children under three years old were 16 % in African Americans and 8 % in Caucasians. In contrast, for children who received a year of daily INH, several studies reported no deaths and no disease, or a reduction of 90 % in the appearance of TB during the first year of treatment, with a protective effect lasting at least 30 years. Most of these studies used INH at 5.0 to 10.0 mg/kg/day, not exceeding 300 mg/day, in a single daily dose for one year (American Thoracic Society 1994, Comstock 1967, World Health Organization 2001).

Current recommendations for preventive therapy are based on a comparative analysis of the risk of administration of INH versus the risk of acquiring the disease. Adults with a positive TST and no clinical or radiographic manifestations, who received INH therapy, have 54 % to 88 % protection against the development of the disease, while children have been reported to have between 90 % to 100 % protection (Hsu 1995, Correa 1997).

INH is the drug of choice for prophylaxis worldwide, and is an extremely effective agent in preventing progression from infection to active disease. The only caveat is that the prevalence of primary INH resistance must be low enough to ensure that the prophylaxis will be effective. This is frequently unknown in several countries or regions, and should be evaluated before establishing a standard preventive treatment regimen in these areas. If the strain isolated from the source case is INH-resistant but still susceptible to rifampicin (RIF), this is then the recommended prophylactic agent.

Studies on the treatment of adults with latent TB demonstrated that six months of INH administration was less effective but more cost-effective than a 12-month treatment. Although there are no comparable data for children, based on the results in adults, many healthcare providers adopted the six-month regimen for children with TB infection. At present, a nine-month duration of INH treatment for children with TB infection is the general recommendation. A period of treatment of 12 months is recommended for patients with HIV co-infection.

Although there are no published studies that demonstrate the effectiveness of twice-weekly preventive therapy for TB infection, this may be justified in certain situations where the risk of progression to disease is high and non-adherence to the daily treatment regimen is suspected.

For childhood contacts of INH-resistant cases, preventive therapy with RIF is generally recommended, but specific efficacy data are still available in the literature.

Treatment for exposure

Although exposed adults are usually not treated, young children should receive chemotherapy during the exposure stage and until infection has been properly excluded.

For recent contacts of patients with contagious TB (i.e. contact within the last three months), INH chemoprophylaxis is indicated even if the TST is negative. This is especially true for contacts that are infected with HIV or for household contacts younger than five years old.

Children treated for exposure should receive at least three months of an effective drug after contact with the source has been interrupted. If TST is negative after this period (i.e. TST < 5 mm), treatment can be stopped. If TST becomes positive, the infection has occurred and treatment must be extended for a total of nine months.

Infection in newborns

Newborns may become infected through the mother or another family member with multibacillary pulmonary TB. In general, they can be treated in the same way as other exposed children, with the addition of pyridoxine to prevent neurological complications of INH treatment. There is no reason to restrict breastfeeding and contact between the infected mother and child must be encouraged.

Management of a neonate whose mother or another household contact has TB depends upon the status of the disease in the mother. The following general recommendations have been elaborated by the American Academy of Pediatrics (American Academy of Pediatrics 2003, Curtis 1984, Starke 1997):

- The mother has a positive TST and no evidence of active disease. Since a positive TST may be evidence of an unrecognized case of contagious TB within the household, careful screening and evaluation of the other members of the household should be performed. Perform a Mantoux test when the infant is aged four to six weeks and again at age three to four months. Consider giving INH (10 mg/kg/day) to the infant if the family cannot be promptly evaluated for the presence of active TB.
- The mother has active disease but is not contagious at the time of delivery. Evaluation of the infant includes chest radiograph and Mantoux test at age four to six weeks; if negative, the test must be repeated at age three to four months and again at six months. INH should be administered even if the

TST result is negative and the chest X-ray does not suggest TB. Progressive disease may not develop until six months of age.

- If the mother is receiving treatment and non-infectious, separation of the mother and infant is not necessary and breastfeeding should not be discouraged. The amount of drug in breast milk is very small, and there has been no good documentation of adverse effects, although the infant should be given pyridoxine. Mothers who have received anti-tuberculosis drugs are much less infectious than those who have not received any treatment, due primarily to the reduction in the bacillary population in the lungs (Correa 1997, Starke 1997).
- The mother has active disease and is contagious at the time of delivery. In this situation, separation of the mother and infant is recommended until the mother is no longer contagious. Thereafter, management is as described above.

Treatment of congenital infection

Congenital TB is not a frequent presentation, but if the possibility is suspected, a prompt Mantoux test and chest radiograph must be performed, and treatment of the infant begun immediately. INH should be administered until the infant is six months old, at which time TST should be repeated. If the TST result is positive, the infant should be treated with INH for a total of nine months.

Safety considerations for treatment of latent tuberculosis

Treatment of childhood TB infection with INH has proven to be very safe. The incidence of asymptomatic elevation in serum liver enzymes in children is usually lower than 2%, and clinical hepatitis is less than 1%. Routine tests of blood chemistry and serum hepatic enzymes are unnecessary unless the child has hepatic disease or dysfunction, or is also taking other potentially hepatotoxic drugs. Medical examinations are recommended every four to six weeks to check for adverse reactions as well as to assure adherence to the treatment. Simultaneous administration of pyridoxine is routinely prescribed only for breastfed babies, pregnant women and persons with poor dietary intake of this vitamin (Pape 1993).

Treatment of infection with a multidrug-resistant strain

The best treatment for latent TB in both adults and children infected with a multidrug-resistant strain (MDR-TB) is uncertain because it requires the use of less effective drugs that are associated with adverse reactions that are both more frequent and more severe. Careful follow-up and observation of the children is rec-

ommended, as none of the second-line drugs have been evaluated for preventive therapy. Drugs have been used in these circumstances include pyrazinamide, fluoroquinolones, and ethambutol, depending on the strain susceptibility pattern. (Correa 1997, Starke 1997).

16.7.2. Treatment of pediatric tuberculosis disease

Treatment of pediatric TB follows the same general principles as the treatment of adults. The specific therapeutic regimen should be individually designed according to available drug susceptibility testing results, the tolerance of the patients for the drugs, and the continuous supply and availability of drugs for the whole duration of treatment (Canetti 1969, Heifets 2003, American Academy of Pediatrics 2003, American Thoracic Society 1994, American Thoracic Society /Centers for Disease Control and Prevention 2001, Blumberg 2004).

Following the standard guidelines for new patients, the child must be given at least three drugs during the first phase of the treatment. As in the HIV co-infected population, injections are avoided in children when possible, and therefore streptomycin, which also has ototoxicity, is not recommended in this age group. The second phase must include two drugs, which can be administered twice a week (Table 16-2).

Table 16-2: Recommended doses in therapeutic regimens for TB in children according to the localization and seriousness of the disease (American Academy of Pediatrics 1994; American Thoracic Society 1994).

Disease localization		1 st phase (month)	2 nd phase (month)	Total (month)
Pulmonary disease	Moderate*	2 HRZ	4 HR	6
	Serious*	2 HRZE (or S)	4 HR	6
Extrapulmonary		2 HRZ	7-10 HR	9-12
Meningitis		2 HRZE	7-10 HR	9-12
Associated HIV	with	2 HRZE	7-10 HR	9-12

H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; S: streptomycin.

Treatment of respiratory disease

Since the '70s anti-tuberculosis treatment has become shorter, but with more drugs included in the treatment regimen. The most commonly prescribed regimen for pulmonary TB in children is a six-month course of INH and RIF supplemented during the first two months with pyrazinamide. This intensive first phase with three drugs is followed by four months of the continuation phase with INH and RIF alone (Vallejo 1994).

Poor adherence to TB treatment can lead to relapse and to the development of drug-resistance. This problem becomes exacerbated in the pediatric population by the unavailability of pediatric formulations for all first-line drugs, the lack of symptomatology and the poor radiographic improvement commonly seen in this age group. To ensure adherence to and completion of therapy, all children must be treated under directly observed therapy (DOT), which is based on the medication delivery by a healthcare worker, a responsible family member or a school employee. DOT as an activity inside DOTS (directly observed therapy of short course) strategy, has proven to be the most effective and safest way to administer anti-tuberculosis therapy (Correa 1997, Kochi 1991, Starke 1995).

There is no data about pediatric regimens using twice-weekly treatment under directly observed therapy (DOT), but in adults these regimens have proved to be as effective and safe as daily therapy. In the published clinical trials the overall success rate has been greater than 97 % for complete clinical and radiographic cure and 99 % for significant radiographic improvement during a two-year follow-up period. The incidence of relevant adverse events, mostly gastrointestinal upset or mild skin rash, was less than 2 %.

Short courses of corticosteroids may be effective for children with enlarged hilar lymph nodes that compress the tracheal bronchial tree causing respiratory distress, localized emphysema, or severe segmental pulmonary disease. The most commonly prescribed regimen is prednisone 1 to 2 mg/kg/day for 4 to 6 weeks with gradual tapering (Starke 2004).

Special situations: HIV, drug resistance

The optimal treatment for HIV co-infected children has not yet been established, although most experts consider that the initial regimens should be the same as those for non HIV-infected children, but extended to nine to 12 months.

When it is possible to obtain cultures from older children, drug susceptibility testing should be performed. However, when an isolate can't be obtained from the child or while waiting for cultures to grow, there are situations that raise suspicions

that the child may be infected with a drug resistant strain that could compromise the efficacy of the standard treatment regimen: an unidentified contagious source, several possible contagious sources in the child's environment, or when the likely source case has a drug-resistant strain.

If the risk for initial INH or other drug resistance is significant, a fourth drug, usually ethambutol, should be given until drug susceptibility information is available. If the strain is eventually shown to be susceptible to INH and RIF the fourth drug can be discontinued (Correa 1997, Vallejo 1995, Vallejo 1996).

For pulmonary disease caused by INH-resistant but RIF-susceptible strains, a nine- to 12-month regimen containing RIF, pyrazinamide and ethambutol or streptomycin is usually highly effective. Although streptomycin is a bactericidal drug, its use in children is restricted due to its parenteral administration and ototoxicity, so ethambutol is preferred.

Treatment of children infected with multidrug resistant TB (MDR-TB) – strains, resistant to at least INH and RIF, is as difficult as in adults. MDR-TB requires the administration of three to six drugs to minimize the probability of failure and relapse, and the selection of the drugs should be based on the results of drug susceptibility testing (Palomino 2000). Drug treatment should last between 12 to 24 months, depending upon the anatomic location of and severity of the disease, and when the patient becomes bacteriologically negative, both by direct smear examination and by cultures, if possible. Drugs associated with frequent side effects, such as cycloserine and ethionamide may be started at low doses and if tolerated, gradually increased to the recommended dose. The use of fluoroquinolones in children remains controversial because of their potential for damaging cartilage growth. However, the later generation fluoroquinolones, such as moxifloxacin, have good bactericidal activity against *M. tuberculosis*, so their use in second-line treatment regimens for pediatric MDR-TB is being recommended. However, the use of fluoroquinolones must be individualized for each case to minimize the risk of cartilage damage.

Treatment of non-respiratory disease

There are virtually no controlled clinical trials comparing different treatments for extrapulmonary TB in children, but, the three-drug, six-month schemes used for pulmonary TB appear to be effective for most forms of the disease. The exceptions are bone and joint involvement and TB meningitis. For bone and joint TB, recommended treatment is for nine to 12 months, while meningitis should be treated for no less than 12 months (American Thoracic Society 1994, American Thoracic Society /Centers for Disease Control and Prevention 2001, Blumberg 2004).

Corticosteroids are useful in the treatment of some children with TB under effective anti-tuberculosis drugs and probably are used more commonly for children than adults with TB (Starke 2004). Corticosteroids are useful when the host inflammatory reaction contributes significantly to tissue damage or impairment of organ function. In these cases, the most commonly prescribed regimen is prednisone 1 to 2 mg/kg/day for 4 to 6 weeks with gradual tapering. There is convincing evidence that corticosteroids decrease mortality rates and long-term neurological sequelae in patients with TB meningitis (Starke 2004).

16.7.3. Surgical treatment

Surgical intervention in children is a rare event. Hemoptysis, though rare in pediatric cases, is the most frequent situation requiring surgical intervention, but surgery may also be indicated to remove tubercular abscesses and close bronchopleural fistulae (Freixinet 1995, Starke 1996).

16.7.4. Monitoring pediatric cases under chemotherapy

Routine examinations and drug toxicity

In children without any co-morbidity, the rate of drug-related adverse effects is low enough to make frequent, routine, biochemical monitoring unnecessary. Hepatotoxicity from INH is age related, and rare in children. However, if the child has had hepatitis or a chronic hepatic illness, it is necessary to obtain baseline serum levels of liver enzymes before initiating TB therapy. When patients or their families report any symptoms that might be attributable to the drugs, a physical examination and serum liver enzyme determinations must be performed. Two- to three-fold elevations in serum liver enzymes are common and, in the absence of other abnormal findings, do not require discontinuation of the drugs. However, the levels should be checked again after several weeks to make sure they are stable.

Mild arthralgias are usually caused by pyrazinamide and are transient, even without discontinuing the drug. Ethambutol is well known for causing blurred or altered vision and color blindness, but ophthalmologic toxicity in children has not been reported with an ethambutol dose of 15 mg/kg/day. Nevertheless, children taking ethambutol should be carefully monitored for decreased visual acuity and color blindness, although in a child less than six years old, it is hard to know if they are having visual side effects. Ethionamide often causes gastrointestinal disorders and can also cause hepatitis. Cycloserine is usually well tolerated by children but can cause changes in mood and a variety of neurological complaints. Several doctors

think that serum cycloserine levels should be monitored whenever the drug is given (Correa 1997). Only RIF is available in pediatric formulation.

Radiographic control

Chest X-rays should be obtained at the time of diagnosis and repeated one to two months after beginning treatment, to ensure that no progression or complications have occurred. When the results are satisfactory, it is not necessary to repeat the chest radiograph until the planned end of the treatment. However, chest radiographs are often not useful to verify treatment success, because radiographic improvement of pulmonary TB and intrathoracic adenitis can occur at different speeds, and is generally very slow.

The majority of children with intrathoracic adenopathy presumably attributable to TB will have abnormal radiographic images during a period ranging from one to three years after successfully completing treatment. For this reason, it is not necessary to achieve a normal chest radiograph before discontinuing treatment. If clinical improvement has occurred after six months of treatment, the drugs can be stopped and the chest radiographs repeated at 6- to 12-month intervals until they become stable (Correa 1997).

16.8. Vaccination

Although BCG vaccination has been in use since 1921, and approximately three billion doses have been administered, its efficacy continues to be debated. Several trials performed to assess the efficacy of the vaccine have produced results that vary from country to country. While controversy exists about its efficacy against pulmonary TB, it is generally accepted that BCG vaccination does not prevent infection with *M. tuberculosis* nor the development of the disease after infection (Trnka 1998). However, two meta-analyses of the various trials concluded that the vaccine is efficacious against miliary and meningeal TB (Rodrigues 1993). Therefore, the major role of BCG is the prevention of severe and life-threatening forms of TB in children (Curtis 1984, Fine 1999, World Health Organization 1982, Young 1986).

The Expanded Program on Immunization from the WHO recommends the administration of BCG only at birth. The vaccine is being used in more than 100 countries. In developed countries, such as the United States, BCG vaccination is currently recommended only in certain situations:

- when the child is exposed to persons with contagious pulmonary MDR-TB, has negative HIV and TST results, and cannot be removed from the exposure;
- the child is exposed to persons with untreated or ineffectively treated contagious pulmonary TB, has negative HIV and TST results, and cannot be removed from the exposure or treated with antitubercular medication.

From birth to two months of age, administration of BCG does not require a prior TST. Thereafter, a TST is mandatory prior to vaccination.

Adverse reactions due to the vaccine include subcutaneous abscess formation and lymphadenopathy. Contraindications to the administration of the vaccine include immunosuppressed conditions, such as primary genetic immunodeficiency syndromes or secondary immunodeficiency, for example from steroid use, and HIV infection. However, in areas of the world where the risk of TB is high, WHO recommends using the BCG vaccine in children who have asymptomatic HIV infection (Dourado 2003, see Chapter 8).

Rare complications of the BCG vaccination, such as osteitis of the epiphyses of the long bones or disseminated BCG, are generally associated with an immunocompromised status and may necessitate administration of anti-tuberculosis therapy, excluding pyrazinamide.

16.9. Prognosis of pediatric tuberculosis

The prognosis for children with TB varies according to the clinical manifestation. In general and under DOTS strategy conditions, primary TB caused by a fully drug-susceptible strain has a more than 95 % probability of being cured, but poor prognosis is associated with disseminated TB, miliary disease and tubercular meningitis. The prognosis of tubercular meningitis varies according to the stage of the disease at the time treatment is started. Stage one has good prognosis, while patients with stage three are usually left with sequelae, such as blindness, paraplegia, deafness, mental retardation, movement disorders, and diabetes insipidus. Higher mortality rates occur in children younger than five years old (20 %) and in those with a prolonged illness of more than two months (80 %) (American Academy of Pediatrics 1994, American Academy of Pediatrics 2000, Correa 1997).

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