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Algorithm for Preventive Therapy of Childhood Tuberculosis

Figure 1
Pathogenesis

I. Portal of Entry

Entry into the body occurs largely by inhalation of aerosolized particles containing 1-3 tubercle bacilli that are deposited in the alveoli. Ghon and Kuedlich showed in 1930 that the primary focus in 2,114 autopsies in children was in the lung in 95.93 percent of case.1

II. Incubation Period

This refers to the period from the time the tubercle bacilli enter the body until tissue hypersensitivity develops, as manifested by a positive tuberculin test. This has been found to range from 19 to 56 days (3-8 weeks); however, the incubation period may be shorter when the inoculum is large.1

"The time interval between the initial infection with tubercle bacilli and the development of an altered tissue reaction to the bacilli and their metabolic products is the incubation period of tuberculosis." M Pardo de Tavera (1975)

III. Immunopathogenesis

There are four stages of the pulmonary pathology as described by Dannenberg.2 In the first stage scavenging nonactivated alveolar macrophages ingest the tubercle bacilli which gets destroyed or inhibited depending on the virulence of the organism and the innate microbicidal ability of the macrophages.

The second stage is the stage of symbiosis. If the original macrophage fails to destroy the bacilli, the bacilli undergo unrestrained replication, eventually destroying the macrophage. Other alveolar macrophages and blood-borne monocytes are then attracted by chemotaxis to wherever the bacilli are released. With time, more and more macrophages and more and more bacilli accumulate in the developing lesion called tubercle or granuloma.3,4

In the third stage, the logarithmic increase in the number of bacilli is inhibited by the development of cell-mediated immunity (CMI) and delayed-type hypersensitivity (DTH). Although the macrophages that first ingest M. tuberculosis may not kill these organisms, they initiate both DTH and CMI, which eventually contain the infection. Infected macrophages present tuberculous antigens to T lymphocytes. T lymphocytes get sensitized, to produce a progeny of similarly reactive cells and secrete lymphokines (IFN gamma and TNF) that activate macrophages. Activated macrophages secrete lytic enzymes and reactive metabolites that greatly enhance killing of bacilli; but if released into surrounding tissue may also cause tissue necrosis. This enhanced microbicidal activity of macrophage comprises cell-mediated immunity.2,3,4

DTH is immunologically the same process as CMI, involving T cells and their cytokines. However, Dannenberg defines DTH "pathologically" as the immunological reaction that causes caseous necrosis, i.e. the death of local macrophages and nearby tissues. Both CMI and DTH inhibit the multiplication of bacilli equally. CMI does so by activating macrophages into killing ingested bacilli and DTH, by killing bacilli-laden non-activated macrophages in nearby tissues to eliminate the intracellular environment which favors bacillary growth.2,3

The pathologic events in the initial tuberculosis infection seem to depend on the balance among the mycobacterial antigen load, cell-mediated immunity and tissue hypersensitivity. When the antigen load is small and the degree of tissue sensitivity is high, a vigorous granulomatous reaction is produced. Tubercle bacilli are killed by activated macrophages, surrounded by fibrous tissue and successfully contained. When the antigen load is high, hypersensitivity reaction produces significant tissue necrosis with characteristic cheese-like (caseous) consistency. In solid caseous material, the tubercle bacilli can survive even for years, but cannot multiply due to anoxic condition, reduced pH and presence of inhibitory fatty acid.3,6

Caseous necrosis, however is inherently unstable and has the tendency to liquefy, especially in the lungs. This comprises the fourth stage, a stage of liquefaction. Liquefaction of the caseous center provides an excellent growth medium for the bacilli. The bacilli multiply extracellularly, producing an increase in population of bacilli. CMI, even if well developed, is frequently ineffective in controlling the large number of bacilli. DTH acts on this large antigen load resulting in cavity formation and destruction of bronchial wall. The bacilli and liquefied caseous material are discharged into the airways and spread to other parts of the lungs and the outside environment.2,3,4

IV. Pathology

The lung lesion of primary tuberculosis is known as the Ghon focus. It is usually located in the subpleural area of the upper segment of the lower lobe or in the lower segment of the upper lobes. It starts as a small, ill-defined area of inflammatory consolidation. Concurrent with the onset of primary infection, the tubercle bacilli, either free or within macrophage are carried via lymphatics to regional (most often hilar and mediastinal) lymph nodes. The primary pulmonary focus, infected lymph nodes and associated lymphangitis form the
**Ghon complex** 3,6. Other authors describe the Ghon complex as a combination of calcified peripheral lung lesions and calcified hilar nodes 4,5.

*M. tuberculosis* bacilli disseminate from these lymph nodes through the lymphatics and blood vessels. Tissues that are highly vascularized or have high oxygen tensions favor retention and bacillary multiplication and these include lymph nodes, kidneys, the epiphysis of long bones, vertebral bodies and most importantly, the apical posterior areas of the lung. The bacilli may cause disease in these sites promptly after the primary infection or lie dormant in tissue macrophages and cause disease many years later 3,5,6.

In most instances, the primary infection is controlled, with a positive skin test as the only evidence of infection. In both the lungs and the lymph nodes, the lesions of the Ghon complex heal by shrinkage, fibrous scarring and calcification. Most of the organism die, but a few may remain viable and reactivate later, if immune mechanisms wane or fail 3,6.

A less common alternative course is **primary progressive tuberculosis** which occurs in situations where the immune response fails to control multi-plication. The Ghon focus in the lung enlarge and may even erode into the bronchial tree. The affected hilar and mediastinal lymph nodes also enlarge, sometimes compressing the bronchi to produce atelectasis of the distal lung. One sequela of this compression is collapse of the middle lobe, the "middle lobe syndrome". The infected lymph nodes may likewise erode into an airway to spread organisms throughout the lung that may render the child potentially contagious.

Miliary tuberculosis refers to infection at disseminated sites where multiple small yellow nodular lesions are produced in several organs like the lungs, lymph nodes, kidney, adrenal, bone marrow, spleen and liver. Progressive disease may involve the meninges and cause TB meningitis 3,4,5,6.

**V. Timetable of Tuberculosis**

Walgren's timetable described the usual early course and timing of the initial infection and its common complications. Figure 1 provides the clinician with a "realistic prognosis, an understanding of what complication to look for and when, and a more productive approach to finding the infectious contact" 1.

The timetable shows that the first 5 years after initial tuberculosis infection in childhood but especially the first year are the time when complications are expected to occur. However, later in life, especially in times of stress, a previously silent or arrested lesion may reactivate and become dangerous to the patient and infectious to others.

For chronic pulmonary TB, the interval between initial infection and disease is markedly variable depending on the age the child acquired the infection; in adolescents the interval is often short but in infants, much longer.

Lesions involving bones and joints seen in 5-10% of infected children do not appear until about a year after infection, at the earliest. Renal involvement appears much later, 5 to 25 years after initial infection. Symptomatic, massive lymphohematogenous spread, i.e. miliary or acute meningeal tuberculosis, is rare and seen in only 0.5 to 3 percent of affected children. When it occurs the usual onset is 2 to 6 months after initial infection; endobronchial tuberculosis develops later.

**Reference:**


**Figure 1. Walgren's timetable of tuberculosis (Modified from Feigin')**
Clinical Manifestations

I. Classification

II. Clinical Forms

A. Pulmonary/Endothoracic TB
   1. Asymptomatic or Latent TB Infection (LTBI)
   2. Primary/Childhood TB
   3. Pleurisy with Effusion
   4. Progressive Primary TB
   5. Endobronchial TB
   6. Miliary TB
   7. Chronic Pulmonary TB
   8. Tuberculoma
   9. Pericardial TB

B. Extrapulmonary TB
   1. TB of the Cervical Lymph Nodes (Scrofula)
   2. TB of the Central Nervous System
      TB meningitis
      Tuberculoma/TB Abscess
   3. Skeletal TB
      TB of bone and joints: TB of the spine
      (Pott’s disease)
      TB arthritis
   4. Gastrointestinal TB
      TB enteritis (tabes mesenterica)
      TB peritonitis
      Hepatobiliary TB
      TB of the pancreas
   5. Cutaneous TB (scrofuloderma)
   6. Ocular TB (phlyctenular kerato conjunctivitis)
   7. Genitourinary TB
      Renal TB
      Genital TB
   8. TB of the Middle Ear

III. Children with Tuberculosis in Special Situations

   Congenital TB: Newborns of Tuberculous Mothers
   Others

Overview

*Mycobacterium tuberculosis* can produce infection and disease in almost every tissue and organ in the body, but the disease is usually the result of dissemination from an initial primary focus. Since infection usually takes place by way of the lower respiratory tract, the lung is the first organ involved and it is here that the initial major manifestations of disease occur.

Distinction must be made between infection and disease. With primary infection, most patients are asymptomatic. When disease is present, early manifestations are mild with nonspecific systemic symptoms of low grade fever, lassitude, easy fatigability, anorexia, weight loss, malaise and night sweats which are common to many illnesses in childhood. With progression and chronicity, symptoms may be respiratory as well as systemic.

I. Classification

The following classification was adopted by the National Consensus on Childhood Tuberculosis in 1997 based on the American Thoracic Society, the Centers for Disease Control and the 3 major stages of TB: exposure, infection and disease. Knowing the category to which the child belongs will determine the appropriate evaluation and treatment.

The criteria for classification of persons exposed to and/or infected with *M. tuberculosis* of the American Thoracic Society (ATS) and Centers for Disease Control (CDC) is based on the bacteriologic and chemotherapy status of the patient. Unlike in adults, the diagnosis of TB in children is difficult and TB infection, which is latent, is confused with TB disease, which has clinical and/or radiologic signs. TB in children is diagnosed based on epidemiological and/or clinical grounds; cultures are rarely available.

Class I (TB Exposure)

- (+) Exposure to an adult/adolescent with active TB
- (-) Signs and symptoms of TB
- (-) Mantoux tuberculin test
- (-) Chest radiograph

Immediately after a child has had significant exposure to an adult/adolescent with active TB disease, the clinician cannot tell whether the child is already infected with *M. tuberculosis*. This is because the development of delayed-type hypersensitivity to tuberculin may take up to 3 months after the infectious droplet has been deposited in the lung, and before the clinical signs and symptoms develop or the chest x-ray becomes positive.

Class II (TB Infection)

- (±) History of exposure
- (+) Mantoux tuberculin test
- (-) Signs and symptoms of TB
- (-) Chest radiograph

This is the pre-clinical state of TB. The risk of developing TB disease is between 5-15% during the first 10 years after primary infection, with the highest risk developing in up to 50% of infants within 3-9 months of infection, 25% in children 1-5 years of age within 1-2 years and 15% in adolescents. This risk to development of TB disease, which may be severe or progressive, depends on several factors such as age, nutritional status, bacteriological status of the adult source and intensity of contact.
Class III (TB Disease)

A child who has active TB has 3 or more of the following criteria:
1. (+) history of exposure to an adult/adolescent with an active TB disease
2. (+) Mantoux tuberculin test
3. (+) signs and symptoms suggestive of TB: one or more of the following should be present:
   - cough/wheezing > 2 weeks; fever > 2 weeks;
   - painless cervical and/or other lymphadenopathy
   - poor weight gain; failure to make a quick return to normal antibiotic therapy (pneumonia, otitis media)
4. abnormal chest radiograph suggestive of TB
5. laboratory findings suggestive of TB (histological, cytological, biochemical, immunological and/or molecular)

A positive culture with or without a positive smear for *M. tuberculosis* is the gold standard for the diagnosis of TB and must be sought for whenever possible.

A child should at least have 3 out of 5 criteria to satisfy a diagnosis of TB disease. (Consensus Statement)

Because of increased susceptibility to the deadly forms of TB, infants or children less than 2 years of age who present with fever, cough, pallor, weight loss, with or without hepatomegaly/splenomegaly should be investigated for miliary TB.

In contrast to early TB, symptoms are very helpful in the diagnosis of extrapulmonary or progressive TB. In addition to the more common and general symptoms as fever, anorexia and/or weight loss, delayed menarche or suppression of menses in girls, signs or symptoms referable to other organ systems may be present.

In the presence of any of the following, the PPS Consensus recommends that the patient be referred to a hospital for evaluation and treatment:
- sinus in the neck
- large painless lymph nodes in the neck, axilla or groin
- angle deformity of the spine
- joint or bone swelling or sinuses
- unexplained abdominal mass or ascites
- change in temperament, fits or convulsions

Class IV (TB Inactive)

A child/adolescent with or without history of previous TB and any of the following:
- (+) previous chemotherapy
- (+) radiographic evidence of healed/calcified TB
- (+) Mantoux tuberculin test
- (-) signs and symptoms suggestive of TB
- (-) smear/culture for *M. tuberculosis*

Disease categories according to the WHO classification are based on treatment/retreatment status, whether there is response or non-response to a particular regimen. (See Appendix I. WHO Disease Classification & the National TB Control Program)

II. Clinical Forms of Tuberculosis

A. Pulmonary/Endothoracic Tuberculosis

1. Asymptomatic (or Latent) Tuberculosis Infection (LTBI)

Asymptomatic or latent tuberculosis infection is defined as infection associated with tuberculin hypersensitivity and a positive tuberculin test but with no striking clinical or roentgenographic manifestations. Occasionally, low grade fever is found, usually by chance.

These children may typically be assessed to belong to Class II.

2. Primary (Childhood) Tuberculosis

Infection in infants frequently results in disease, with local progression and dissemination. The younger the patient, the greater the risk of progressive disease until the age of 5 years. When disease occurs it is usually the childhood type of pulmonary tuberculosis. When confined to the lungs in this age group, spontaneous healing occurs; a high frequency of relapse may develop with chronic disease.

The primary complex is composed of the primary focus, lymphangitis, and regional lymphadenitis. The hallmark of the initial disease is the relatively large size of the adenitis compared with the relatively insignificant size of the initial focus in the lungs.

There are no striking clinical manifestations although young infant and adolescents are more likely to have significant signs and symptoms than school-aged children. Non-productive cough, mild dyspnea, cervical lymphadenopathies are the most common clinical symptoms and signs. Some infants have difficulty gaining weight or have a failure to thrive pattern.

From hereon, the symptomatic child with disease and complications from its progression, will belong to Class III until the disease becomes inactive (class IV) with time and/or with partial treatment.

3. Pleurisy with Effusion

Tuberculosis pleurisy with effusion is an early complication of primary infections. Pleural effusion may be localized or generalized, unilateral or bilateral. It is the localized pleural effusion, which frequently accompanies the primary focus and is considered a component of the primary complex. Hypersensitivity to tuberculin is another factor implicated in the pathogenesis of pleural effusion in tuberculosis.
The onset of pleurisy is usually abrupt resembling bacterial pneumonia, with fever, chest pain, shortness of breath and on physical examination, dullness to flatness and diminished breath sounds. Fever may be high and in untreated cases, last for several weeks. Lateral roentgenographic views are helpful in confirming the presence of pleural fluid. Obliteration of the costophrenic sinus may be the earliest radiologic sign of minimal fluid accumulation. Moderate effusion causes layering of fluid density along the lateral chest wall. Massive effusion may occupy one hemithorax, which demonstrates a uniform density and dis-placement of the mediastinum towards the contralateral side.

4. Progressive Primary Tuberculosis

Latent primary infection and childhood TB with chronicity becomes progressive, resulting in an area of advancing pneumonia, or it may result in acute dissemination with meningeal or other localizing manifestations. This is a serious complication in which the primary pulmonary focus, instead of resolving or calcifying, enlarges steadily and develops a large caseous center. More severe fever, cough, malaise and weight loss as well as classical signs of cavitation often accompany a progressive primary lesion. Lung findings consist of crepitant rales and/or diminution of breath sounds over the area. Lymph node enlargement or lymphadenopathy often accompany the previously mentioned manifestations.

5. Endobronchial Tuberculosis

Bronchial obstruction can be due to enlargement of peribronchial lymph nodes. As the nodes enlarge, they frequently impinge upon the neighboring regional bronchus, thus compressing it and causing diffuse tuberculous inflammation of its wall even to the point of obstructing the lumen. Three possible immediate results of the bronchial obstruction are the following:

- Sudden death by asphyxia
- Obstructive hyperaeration of a lobar segment, a lobe or even an entire lung (emphysema)
- Segmental lesions representing mainly atelectasis and almost always involving the very segment occupied by the pulmonary focus in endo-bronchial tuberculosis. Infected nodes adhere to an adjacent bronchus and with extension of the disease through the airway wall of the mucosa, obstruction of the lumen results in atelectasis. This is more likely to be present in the right lung, particularly in the right middle lobe and to a lesser extent, the right upper lobe. The right middle lobe is most vulnerable when there is enlargement of the hilar lymph nodes.

Signs and symptoms include moderately high fever, anorexia, night sweats, loss of weight and paroxysmal cough ending in cyanosis. Crepitant rales and expiratory wheezes are likewise noted, often mistaken for per-tussis or bronchial asthma.

Bronchial obstruction may eventually lead to any of the following: complete re-expansion of the lung with resolution of roentgenographic findings: disappearance of the segmental lesion with residual calcification of the primary focus or the regional lymph node; or scarring and progressive contraction of the lobe or segment, usually associated with bronchiectasis. The middle lobe syndrome may occur as a consequence of se-condary infection in the obstructed bronchiectatic segment.

6. Miliary Tuberculosis

Miliary tuberculosis is a form of generalized hematogenous tuberculosis due to massive invasion of the blood stream by the tubercle bacilli. It arises from the discharge of a caseous focus, often from a lymph node, into the blood vessel (such as a pulmonary vein). It is most common during the first 3-6 months after infection in infants.

Clinical symptoms may start acutely or insidiously, with respiratory symptoms. There may be sudden onset of high fever, dyspnea, cough, and prostration soon followed by symptoms referable to other organs invaded; in insidious forms, symptoms of tuberculosis are exacerbated and then followed by dyspnea. Other clinical features are crepitant rales, splenomegaly, hepatomegaly and later, signs of meningeal irritation. Chest roentgenogram show millet seed densities all over the lung fields.

The pulmonary presentation can explain why miliary TB is often discussed under pulmonary or endothoracic tuberculosis.

7. Chronic Pulmonary Tuberculosis

The traditional terms used are chronic pulmonary tuberculosis (or reinfection or adult tuberculosis). This is the type of disease seen in a host previously sensitized by earlier tuberculosis infection. It is characterized by apical or infraclavicular infiltrates often with cavitation and no hilar lymphadenopathy. This is more common in adolescents than in younger children especially when the initial infection has been acquired near puberty.

Clinical manifestations include chronic or persistent cough, prolonged fever, chest pain, hemoptysis and supraclavicular adenitis. Most of these features, though, improve within several weeks of starting effective treatment, but the cough may persist for several months.
8. Tuberculosis

Asymptomatic rounded lesions may develop as a residuum of parenchymal disease in the initial infection or as caseation. Tuberculomas may form with small caseous or granulomatous tissue surrounded by concentric fibrous tissue sometimes with calcification, often confused with cancer.

This is an uncommon condition, complicating only 0.4% of untreated tuberculous infections in children. It is due to direct invasion or lymphatic drainage from caseous subcarinal nodes, serofibrinous or hemorrhagic fluid accumulating between the visceral and parietal surfaces of the pericardium. Sometimes extensive fibrosis leads to obliteration of the pericardial sac, with development of constrictive pericarditis some years later.

The presenting symptoms are usually nonspecific and include low-grade fever, anorexia, poor weight gain, but rarely chest pain. On examination, a pericardial friction rub may be appreciated. When pericardial effusion is already present, distant heart sounds, tachycardia, and narrow pulse pressure are noted. The diagnosis is established by examination of the pericardial fluid, which is usually sanguineous, with a predominantly lymphocytic cellular reaction. When Ziehl-Neelsen stains of pericardial fluid are negative, pericardial biopsy has been suggested as having higher yield.

9. Pericardial Tuberculosis

Other endothoracic forms include: myocardial and pericardial tuberculosis secondary to direct spread from mediastinal glands by direct invasion or by lymphatic spread. Pericardial tuberculosis is an uncommon condition complicating only 0.4% of untreated tuberculous infections in children. It is due to direct invasion or lymphatic drainage from caseous subcarinal nodes, serofibrinous or hemorrhagic fluid accumulating between the visceral and parietal surfaces of the pericardium. Sometimes extensive fibrosis leads to obliteration of the pericardial sac, with development of constrictive pericarditis some years later.

The presenting symptoms are usually nonspecific and include low-grade fever, anorexia, poor weight gain, but rarely chest pain. On examination, a pericardial friction rub may be appreciated. When pericardial effusion is already present, distant heart sounds, tachycardia, and narrow pulse pressure are noted. The chest roentgenogram often reveal "cardiomegaly". ECG changes include diminution in the amplitude of the QRS complex and abnormalities of the S-T segment and T waves. The diagnosis is established by examination of the pericardial fluid, which is usually sanguineous, with a predominantly lymphocytic cellular reaction. Pericardial fluid should be inoculated directly into guinea pigs. When Ziehl-Neelsen stains of pericardial fluid are negative, pericardial biopsy has been suggested as having a higher yield.

B. Extrapulmonary Tuberculosis

1. Tuberculosis of the Cervical Lymph Nodes (Scrofula)

This is the most common form of extrapulmonary TB in children and oftentimes referred to as scrofula.

"Cervical lymphadenitis is not common before the age of 2 years and is uncommon in infancy. Contrary to prevailing opinion, enlarged cervical lymph nodes in Filipino children are more often caused by infections other than tuberculosis." M. Pardo de Tavera (1975)

Through direct extension from a primary pulmonary infection, the cervical chain of nodes becomes the most commonly affected. This is often unilateral but bilateral involvement may occur due to crossover drainage patterns of lymphatic vessels in the chest and lower neck. The cervical nodes may also be involved from other tuberculous foci such as the nasopharynx, middle ear or tonsils. However, one has to remember that cervical lymph nodes may be normally palpable in young children, or can also be caused by infections other than TB such as carious teeth, infected tonsils, acute upper respiratory tract infections and Hodgkin's disease. Hence, a diagnosis of tuberculosis should be supported by a positive tuberculin test and the other criteria for diagnosis such as excisional biopsy and culture and fine needle aspiration cytology and not just based on the presence of enlarged lymph nodes.

Signs and symptoms are absent. Involved superficial lymph nodes are painless, firm, discrete and movable, becoming adherent to each other and anchored to the surrounding tissues and skin as they enlarge. Occasionally, the clinical picture may simulate acute respiratory infections with rapid enlargement of nodes, pain and fever. If left untreated, it may either resolve or may progress to caseation and necrosis of the lymph node, which can rupture and result in a draining sinus tract. The latter behaves indolently and produces a disfiguring scar (scrofuloderma).

Primary tuberculosis of the tonsils begins as a painless swelling of one tonsil, sometimes with an ulcer or yellowish node with associated enlargement of the regional lymph node.

2. Tuberculosis of the Central Nervous System

Tuberculosis meningitis is the most common type of tuberculosis of the nervous system. The disease complicates 0.3% of untreated TB infections, which may develop three to six months after initial infection. Below the age of three years, it is the most common cause of
mortality from TB. It is frequently seen in the first six years of life, though rare in the first four months. It may accompany miliary tuberculosis in approximately 50% of cases.

Meningitis is always secondary to a tuberculous process elsewhere in the body, the primary lesion being in the lungs or in peribronchial and mediastinal lymph nodes in 95% of cases. However, in many cases by the time the meningitis develops, the original focus in the lungs may no longer be demonstrable.

From the primary site, the tubercle bacilli reach the central nervous system via the bloodstream during its lymphohematogenous spread. In the brain, they may lie dormant in the choroid plexus or in the subcortical area until a later injury to the head. It may also be dislodged into the subarachnoid space and infect the meninges. However, in most cases during the lymphohematogenous spread, the bacilli are discharged into the subarachnoid space where they invoke encephalitis. A gelatinous exudate forms around the brain stem resulting in the involvement of the cranial nerves III, VI, VII and the optic chiasm as well as the obstruction of the basal cisterns which leads to hydrocephalus. Arteritis leads to thrombosis and consequent infarction.

Onset of tuberculous meningitis is usually gradual occurring over a period of about 3 weeks. The clinical course is divided into 3 stages namely: an early stage of irritability, the pressure or convulsive stage and the paralytic or terminal stage, respectively. Patients in the first stage may present with apathy, vomiting, irritability and headache. After 1-2 weeks, the second stage begins abruptly with meningeal signs such as lethargy, neck stiffness, seizures and cranial nerve palsies. The third stage is characterized by posturing, profound neurologic and sensorial changes with deterioration of vital signs, and eventually death. Several studies reveal that the main clinical symptoms and signs present in such patients are altered sensorium and focal neurological signs.

Chest radiographs may be normal but oftentimes reveal changes typical of primary TB or a miliary pattern. The tuberculin skin test is of limited diagnostic value. It is very useful if positive; if negative, it does not rule out tuberculous meningitis.

Diagnosis usually rests on clinical grounds and a CSF examination. Performing a lumbar puncture is the most important laboratory test. The spinal fluid is usually clear but with an increased opening pressure. It contains 50-500 WBC/mm³, with polymorphonuclears predominant in the early phase and lymphocytes later in the disease process. CSF sugar is low and protein markedly elevated at which time the fluid develops pellicle on standing. The demonstration of acid-fast bacilli (AFB) on the CSF should be diagnostic for the disease; however, only in a small minority of patients can it be found.

Computed tomography or MRI of the brain has its place in the evaluation of patients with TB meningitis especially those with hydrocephalus who may need shunting procedures. Initially, results may be normal during the early stages of the disease but with progression, commonly reveal basilar enhancement and communicating hydrocephalus with signs of cerebral edema or early focal ischemia. A variety of new tech-niques such as PCR, ELISA, and latex agglutination have been used to search for mycobacterial antigens in the spinal fluid. Some of these have been proven successful in a small sample of patients.

Tuberculoma/TB Abscess. Other forms of tuberculosis of the central nervous system include tuberculoma and tuberculous abscess, both behaving as intracranial space occupying lesions, although the former is more common than the latter. Tuberculomas occur most often in children younger than 10 years and are located at the base of the brain around the cerebellum. Manifestations include headache, convulsions, fever and signs and symptoms referable to a tumor or brain abscess. The spinal fluid findings in well-encapsulated tuberculoma may be within normal limits and this may be diagnostic dilemma to the clinician. Recognition of such forms requires careful evaluation including inquiry about exposure to tuberculosis, a tuberculin skin test and chest roentgenography. Consequently, appropriate chemotherapy can be initiated before neurosurgical intervention is done.

3. Skeletal Tuberculosis

Tuberculosis of the bones and joints occurs in 1-6% of children whose primary infection remains untreated, occurring one to three years after the initial infection. This usually results from lymphohematogenous seeding of the bacilli during the primary infection or may develop as a direct extension from a caseous regional lymph node or by extension from a neighboring infected bone. Young children are more vulnerable to suffer from this form than older ones because of increased blood flow in growing bones. The lesion usually starts as an area of endarteritis in the metaphysis of the long bone, whose blood supply is more abundant.

Most commonly affected are the weight bearing bones and joints specifically the vertebrae causing TB of the spine or Pott's disease. There is a predilection for the lower thoracic, upper lumbar and lumbosacral vertebrae. Frequently, a history of trauma may be elicited as a contributory factor, either activating a quiescent lesion or just simply drawing attention to the process. Multiple vertebral involvement is more common than affection of a single vertebral body.

Serious complications such as paravertebral abscess
Tuberculous arthritis is rare in children. Joints of the upper extremities are the only ones affected with monoarticular involvement.

4. Gastrointestinal Tuberculosis

Tuberculous enteritis may occur after ingestion of tubercle bacilli or as part of generalized lympho-hematogenous spread. Primary TB of the intestinal tract is uncommon in the Philippines because Filipinos are not fresh milk drinkers and because of widespread milk pasteurization. Occasionally, tuberculous enteritis, although rare, accompanies extensive pulmonary cavitary involvement of the intestinal tract commonly the ileocecal area with extension to the mesenteric lymph nodes and peri toneum results from ingestion of bronchial secretions containing tubercle bacilli from a caseous pulmonary focus. The bacilli are taken up by the lymphoid tissues, giving rise to local ulcers followed by mesenteric lymphadenitis and sometimes peritonitis.

Symptoms and signs include vague abdominal pain, intussusception, blood in the stool and sinus formation after an uncomplicated appendectomy. Enlarged caseous and calcified mesenteric lymph glands (tubes mesentericae) are often accidentally discovered on roentgenogram of the abdomen as "shadows of increased density." Inciting local inflammatory reaction, they become matted and result in adhesions interfering with intestinal motility producing intestinal obstruction or compression of the portal vein giving rise to ascites and dilatation of the superficial abdominal veins.

Tuberculous peritonitis is commonly due to rupture of a caseous abdominal lymph node and less frequently from a focus in the intestine or fallopian tube. Clinically, it is classified into "plastic" and "serous" types, the former being less common and characterized by tender abdominal masses and a doughy abdomen; the latter by ascites and signs of peritonitis. Symptoms of fever, abdominal pain, weight loss, anorexia and clinical evidence of ascites are common.

Hepatobiliary tuberculosis. A subset of patients with extrapulmonary tuberculosis have the infection confined solely and predominantly in the liver or biliary tract. Majority of patients present with non-specific symptoms such as fever, malaise, fatigue, night sweats, anorexia and weight loss. Those who have prominent hepatic complaints may manifest with jaundice, abdominal pain, hepatosplenomegaly and ascites. This form of infection is referred to as primary miliary tuberculosis of the liver. A report by Alvarez and Carpio described the clinical and histologic features of 130 patients aged 11-30 years with a 2:1 male preponderance. The patients had localized hepatobiliary tuberculosis, and were seen over a 20-year period at the Santo Tomas University Hospital in Manila. In 82% of cases, the diagnosis was clinically suspected prior to histologic confirmation. The two major forms of presentation included: a) hard nodular liver, fever and weight loss simulating cancer in 55% of patients, and b) chronic recurrent jaundice, mimicking extrahepatic obstruction in 35%. Symptoms were generally present for 1 to 2 years prior to diagnosis.

Tuberculosis of the pancreas. This is a rare condition and occurs secondarily to generalized tuberculosis and occasionally in far advanced cases. Gonzales reported in 1989 the case of a 13-year old male from Pampanga presenting with abdominal enlargement, ascites, hepatomegaly and uncontrolled diabetes mellitus unresponsive to regular insulin. Malignancy of the head of the pancreas was entertained. Exploratory laparotomy revealed the whole pancreas to be multinodular and firm; the liver was not enlarged but with two hard nodules and the gallbladder was distended with dilated common bile duct. Review of the history and subsequent chest roentgenogram of the mother revealed far advanced tuberculosis. He was treated with triple anti-TB drugs with good clinical response and complete resolution of polyphagia, polydipsia, and polyuria.

Although involvement of the liver, spleen, bowel and mesenteric lymph nodes is common in miliary tuberculosis, pancreatic involvement was seen in only 4.7% of 297 autopsy cases of miliary tuberculosis.
5. Cutaneous Tuberculosis

Manifestations in children are based on classification designed earlier for adults: lesions by inoculation from an exogenous source; lesions due to hematogenous dissemination; lesions arising from an endogenous source; and erythema nodosum.

The skin lesions associated with the primary complex may be caused by direct inoculation of tubercle bacilli into a traumatized area. The wound is slow to heal, painless with regional lymphadenitis.

Scrofuloderma indicates tuberculosis of the skin overlying a caseous lymph node that has ruptured to the outside, leaving an ulcer or a sinus. Frequently, the lesions are in the cervical area but may also involve the inguinal, submandibular and axillary groups. Cutaneous lesions resulting from hematogenous spread may be papulonecrotic tuberculids or tuberculosis verrucosa cutis. Papulonecrotic tuberculids are miliary tubercles in the skin resembling the small lesions of chicken pox although more indurated, while tu-berculosis verrucosa cutis are wart-like lesions appearing on the arms or legs.

Erythema nodosum is a common manifestation of hypersensitivity to tuberculin. It occurs mostly in teenage girls and is characterized by large, deep, painful indurated nodules on the skin, thighs, elbows and forearms. The nodules change from light pink to a bruise-like color. Erythema nodosum manifests during febrile episodes and systemic toxicity is seen after initial infection. This cutaneous lesion is seen not only in tuberculosis but also in other infectious conditions such as streptococcal, meningococcal, fungal as well as drug reactions.

6. Ocular Tuberculosis

Ocular tuberculosis is uncommon in children. When it does occur, it frequently involves the conjunctiva and the cornea in the form of conjunctivitis and phlyctenular keratoconjunctivitis. The conjunctiva can serve as the portal entry for the bacilli, especially after trauma. A local reaction is induced in the form of unilateral lacrimation and reddening, with subsequent formation of yellowish-gray nodules on the palpebral conjunctiva. Enlargement of the preauricular, submandibular, and cervical lymph nodes are com-monly noted. In patients with pulmonary and systemic tuberculosis, choroiditis is the most common ocular manifestation. A tuberculin test and biopsy with culture can be performed to confirm the diagnosis. The specificity of the PPD skin test for Mycobacterium tuberculosis increases with larger skin reactions and with a history of exposure to an active case of tuberculosis. Phlyctenular keratoconjunctivitis is considered a hypersensitivity reaction to tuberculin with the formation of small, grayish, jelly-like nodules usually clustered on the limbus and surrounded by dilated conjunctival vessels. Pain and photophobia are observed and the lesions may recur for weeks, affecting one or both eyes. Tuberculous involvement of the ciliary body, iris, uvea and TB presenting as orbital mass are rare clinical entities.

7. Genitourinary Tuberculosis

Renal tuberculosis is an uncommon complication of primary tuberculosis occurring very late, up to 15-20 years after primary infection. However, TB bacilli can be recovered from the urine of patient with miliary tuberculosis and in some cases with pulmonary tuberculosis. Hematogenous spread can give rise to tubercles in the glomeruli, with resultant caseating sloughing lesions which discharge TB bacilli into the tubules. Infection can be unilateral or bilateral and can spread caudal to involve the bladder. The disease can be insidious in onset and has strikingly few specific symptoms. In 75% of patients, however, they would present with symptoms related to urinary tract inflammation such as dysuria, hematuria, sterile pyuria and flank pain.

It should be suspected in the presence of destructive pulmonary tuberculosis with persistent, painless, sterile pyuria with associated albuminuria and hematuria. Repeated cultures of the urine are advisable for those with persistent pyuria, a complete urologic investigation is mandatory. Children whose urine reveal presence of tubercle bacilli are considered to be highly infectious and should be isolated until their urine is sterile.

Genital tuberculosis is uncommon in both sexes before puberty. It may either arise as a metastatic lesion during lymphohematogenous spread or by direct extension from an adjacent lesion of bone, gut or the urinary tract. Frequently, other forms of TB accounts with initial infection, such as pleural effusion also are present. In females, the fallopian tubes are most frequently involved (90-100% of cases), followed by the endometrium (50%), ovaries (20-30%) and cervix (2-4%). Signs and symptoms include lower abdominal pain, amenorrhea, a lower abdominal mass and free peritoneal fluid. TB of the external genitalia has been seen as a ma-nifestation of child abuse.

Males may develop primary tuberculosis of the penis after ritual circumcision manifesting as massive inguinal lymphadenopathy. Epididymitis or epididymo-orchitis can likewise occur characterized by a gradual onset of nodular painless swelling of the scrotum with a dragging pain in the groin.

8. Tuberculosis of the Middle Ear

Tuberculosis of the middle ear is a relatively rare manifestation of the disease in the West but not in developing countries where it is considered in the differential diagnosis.
diagnosis of chronic otitis media in TB patients, or in those who have no evidence of TB elsewhere and whose otitis do not improve with the conventional medical treatment. It may occur either as a primary focus in the area of the Eustachian tube or as a metastatic lesion from a primary focus elsewhere. The primary focus is always unilateral and involves the pre-auricular lymph nodes or the anterior cervical chain. Patients typically have a chronic tympanic membrane perforation and ear drainage associated with progressive and profound hearing loss. Presence of a facial nerve paralysis is highly suggestive of the disease. Essential to its diagnosis is doing a tuberculin skin test, operative biopsy, smears and cultures of otic secretions for mycobacteria.

III. Children with Tuberculosis in Special Situations

Congenital Tuberculosis; Newborns of Tuberculous Mothers

The reliance on chest radiographs for diagnosis of pulmonary tuberculosis in pregnant women has limited identification and therefore treatment of active cases. Congenital TB is rare or probably often remains unrecognized. It is associated with TB of the placenta or acquired in utero (prenatal transmission), during labor or delivery (perinatal transmission). Hematogenous or transplacental route occurs through the umbilical vein (liver primary complex); fetal aspiration or ingestion of amniotic fluid (lung or gas-trointestinal primary complex); and contact with infected secretions during delivery in the presence of maternal genital TB.

In a review of 29 cases31 half of the mothers were asymptomatic. All 14 examined had genital TB. In another series of 59 cases32, the infants presented with respiratory distress (76%), hepatomegaly/splenomegaly (65%), fever (57%). Other signs and symptoms, such as poor feeding, lymphadenopathy and lethargy/irritability occur in about a third of cases; abdominal distention and failure to thrive noted in less.

Other than TB in pregnancy and lactation, special situations seen in children that can present problems in recognition and management include: TB in the immunocompromised, in patients with liver disease, patients with drug-induced hepatitis, renal impairment or renal failure and in the presence of (multi)drug resistance.

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Radiologic Findings in Tuberculosis

Primary Tuberculosis
A. Parenchymal Involvement
B. Lymph Node Involvement
C. Airway Involvement
D. Pleural Involvement
E. Resolution of X-ray Changes

Postprimary Tuberculosis
A. Pulmonary Tuberculosis
   1. Local Exudative Tuberculosis
   2. Local Fibroproductive Tuberculosis
   3. Cavitation
   4. Acute Tuberculous Pneumonia
   5. Miliary Tuberculosis
   6. Tuberculous Bronchiectasis
   7. Tuberculous Bronchostenosis
   8. Tuberculoma
B. Extrapulmonary Tuberculosis
   1. Musculoskeletal Tuberculosis
   2. Central Nervous System
   3. Abdominal Tuberculosis
   4. Renal Tuberculosis

Overview

Chest radiography still has its value in the diagnosis of TB. It is helpful in localizing the site of TB lesions. Although not specific for the diagnosis of pulmonary TB, it becomes important in the diagnosis of pulmonary TB in places where prevalence of TB is high and where facilities for bacteriologic examination are not easily available.

Radiographic evidences seen in x-ray studies parallel the pathologic changes of tuberculous infection. These are divided into 1) initial exposure or primary tuberculosis and 2) postprimary or primary progressive tuberculosis. Reactivation of previous infection or progression of an initial infection exemplifies the latter. In radiologic studies, lateral projections are important for complete and accurate identification and interpretation of the primary complex. Partially calcified mediastinal nodes may be visible only in lateral projections.

The most common cause of calcification in children is tuberculosis. However, other diseases such as histoplasmosis, coccidioidomycosis and aspergillosis may also produce intrathoracic calcifications that cannot be differentiated by radiograph from those due to tuberculosis. Calcifications can also be demonstrated in the nodes regional to inoculations with BCG vaccine. These, however, tend to disappear more quickly than those associated with natural infections.

There are no pathognomonic radiographic findings. Perhaps the only finding that may be highly suggestive of tuberculosis in infants and children is the uniform stippling of both lungs found in miliary tuberculosis.

Special imaging techniques such as computed tomography and magnetic resonance imaging may be of particular value in defining nodules, cavities cysts, calcifications, contours of large bronchi and vascular details in lung parenchyma. Bronchography may be useful in the definition of bronchial stenosis or bronchiectasis.

"A clear chest x-ray does not rule out the existence of a small focus of progressive tuberculosis; nor are there pathognomonic roentgen features in a fresh primary tuberculous complex. Moreover, not all shadows are tuberculous infiltrates."

I. Primary Tuberculosis

In the same way that clinical manifestations of the initial tuberculous infection are meager or absent, there are usually no abnormal radiologic signs in the thorax and the sole evidence of infection is a positive tuberculin test. The initial radiographic picture, whether in a child or adult, is usually parenchymal infiltration accompanied by ipsilateral lymph node enlargement. Lymph node changes tend to persist longer than the parenchymal shadows.

In primary tuberculous infection, the radiologic patterns reflect the development of the pathologic complex seen with initial exposure to the tubercle bacilli. The infection, being primarily spread by inhaled droplet, is seen mostly in the lung. In its complete form, the primary complex is composed of the following; however not all features are necessary to make the diagnosis.

- size and shape in the radiolucent lung,
- enlarged regional nodes,
- lymphangitis that produces linear shadows of increased density connecting the pulmonary focus and the regional nodes, and
- a localized pleural effusion that appears as a shadow of increased density in the pleural space contiguous to the primary focus

As a rule, pleural exudates and the lymphangitis are not clearly seen. Common radiologic findings are enlarged retrocardiac lymphadenopathy in 70% of cases, hilar adenopathy with pulmonary infiltrates in 20% and pleural effusion. Chest radiographs may be normal in up to 10% of patients who have proven primary tuberculosis.

Hilar adenopathy has a specificity of 36%. Because of its low specificity, this radiologic finding should not
be used as a sole basis initiating treatment, without other manifestations suggesting tuberculosis. The lymphatic drainage of the lungs occurs predominantly from left to right, and therefore, the nodes in the right upper paratracheal area appear to be the ones most often affected.

Many primary lesions are subpleural and the lymphatic drainage of the apical pleura is in the cervical nodes. The primary foci can look like any pneumonia and can be situated anywhere. All areas of the lung may be involved.

The principal components of the primary complex and their fate are discussed further below.

A. Parenchymal Involvement

The parenchymal reaction typically is that of acinar consolidation which is usually homogenous in density with ill-defined margins, except where it abuts against a fissure. It predominantly involves the upper lobes with preferential location between anterior or posterior segments and between right and left. Quite frequently, it also involves the apex of a lower lobe.

Atelectasis is important in the production of massive shadows. It frequently affects the anterior segments of the upper and middle lobes of the right lung due to bronchial compression by enlarged lymph nodes. There is surprisingly little shift in the heart and other mediastinal structures; instead, the healthy lung on the same side expands and fills in the space previously occupied by the collapsed segment. Lobar involvement is most probably a combination of parenchymal consolidation and parenchymal atelectasis. An entire lobe, often the right middle lobe, may be affected.

Large primary foci and their perifocal reactions may occupy all or most of a lobe and obscure the lymphangitis and pleural exudate. Perifocal shadows may represent pneumonic consolidation, atelectasis or pleural exudate, singly or in combination. With the gradual clearing of the perifocal shadows, the pulmonary lesions obscured earlier by them become visible, or may never be seen. In other cases, large calcifying pulmonary foci may dwarf the remainder of the tuberculous complex. Cavitation of the primary focus with a perifocal exudate may occasionally be seen but is considered a rare manifestation of pulmonary tuberculosis in infants and children.

B. Lymph Node Involvement

Hilar or paratracheal lymph node enlargement is the radiologic finding that clearly differentiates primary from postprimary tuberculosis. It is usually unilateral. Highly suggestive is the large size of the adenitis relative to the insignificant size of the primary lung focus.

C. Airway Involvement

Tracheobronchial involvement is a common occurrence and in the majority is usually the result of compression of bronchi by enlarged lymph nodes. Bronchial obstruction due to tuberculous lymph nodes may present radiographically as:

Hyperaeration - It may occur in a lobar segment, a lobe or even an entire lung. Roentgenograms, best taken on expiration show hyperaeration which usually without mediastinal displacement, probably because of fixation of the tuberculous mediastinal nodes.

Segmental atelectasis - Described as fan-shaped homogenous density, which most commonly occurs at the middle lobe.

Collapse-consolidation lesions - A roentgenographic finding in which there is only conspicuous atelectasis and consolidation as the salient pathologic process. The volume of the segment is undiminished or seems increased.

D. Pleural Involvement

Pleurisy is so common in primary tuberculosis that it should be considered a component of the complex rather than a complication. It may appear as a localized pleural effusion contiguous to the primary foci, become evident many months after the appearance of tuberculosis in the lung, or manifest as a localized, pleural thickening late in the disease. The pleural effusion may also be generalized, unilateral or bilateral as seen more commonly in progressive type of pulmonary tuber-culosis. It may obscure the underlying pulmonary changes, especially when it is large.

E. Resolution of Radiologic Changes

Due to the great variation in the velocity of healing in the different components of each complex, healing may present a wide variety of findings in different cases. Resolution may begin in the different stages of healing: during fibrosis, hyalinization or calcification in different parts of the complex.

In the small proportion of children with radiologic evidence of the disease, clearing usually occurs within 6 months to 2 years after institution of therapy. Complete resolution without apparent residual is seen in the majority of cases. In some cases, atelectasis remains owing to residual lymph node enlargement. A significant percentage of children who have had atelectasis during the active stage of the disease have residual bronchiectasis in the affected areas.

II. Postprimary Tuberculosis

A. Pulmonary Tuberculosis

In chronic pulmonary tuberculosis, the disease tends
to localize in the apical and posterior segments of the upper lobes and involves the right lung more than the left. Lymph node enlargement is not a feature. The radiologic pattern may be highly suggestive, but it is not diagnostic and is simulated by several factors of mycotic, bacterial, viral and parasitic etiology. The following are radiologic features seen in pulmonary tuberculosis:

1. Local Exudative Tuberculosis

The x-ray pattern is of acinar consolidation, patchy or confluent in nature, especially in the apical and posterior segments of an upper lobe or the superior segment of a lower lobe. Cavitation may be present.

2. Local Fibroproductive Tuberculosis

The relatively poor definition of the exudative lesion is replaced by a more sharply circumscribed homogenous shadow, usually somewhat irregular and angular in contour. Cavitation may be seen. Healing occurs by fibrosis and the resultant cicatrisation may result in loss of volume. If there is significant volume loss, compensatory signs may become evident such as elevation of the ipsilateral hilum, overinflation of the rest of the affected lung, and in some cases, in bullae formation. This pattern is seen more commonly in chronic pulmonary TB.

3. Cavitation

The wall of an untreated tuberculous cavity is moderately thick, and its inner surface is fairly smooth. An air-fluid level is seldom seen. With adequate therapy, a cavity may disappear or regress into a paper-thin, air-filled cystic space. Cavitation is seen both in progressive and chronic types of pulmonary tuberculosis.

Caseous material in a tuberculous focus may simulate cavitation because of its high lipid content that produces a shadow that is slightly less dense than that of the wall. An aid to differentiation is the contrast between the inner wall and the central radiolucency. Air in apposition to a wall tends to show a sharper definition than when the interface is liquid against solid.

4. Acute Tuberculous Pneumonia

Characteristically, bronchogenic spread leads to the formation of multiple small acinar shadows. Extension of the disease may be indistinguishable from that caused by other bacteria. An open cavity or discrete acinar shadows in parts of the lung remote from the massive consolidation suggest that the cause is tuberculous in origin.

5. Miliary Tuberculosis

In the event of an explosive massive spread into the bloodstream, both lungs are evenly seeded with innumerable foci of approximately the same size. At first these lesions are too small to be visualized. The pattern may not become apparent until several weeks after the patient is seen. The lesions require at least 2½ weeks to become perceptible and first appear as difficult to distinguish nodule of a uniform 2mm size.

As the foci become larger and older, multiple small shadows appear which stipple both lungs more or less uniformly ("millet-seed" densities). This stippling of the lungs is the most diagnostic radiologic change in pulmonary tuberculosis during infancy and childhood. Later, these enlarge and coalesce, producing a richly stippled pattern ("snowstorm effect").

With adequate treatment, clearing is quite rapid and without residua. Considerable improvement may be observed within 5 weeks after initiating treatment, while clearing is complete in 7-22 months with a mean of 16 weeks.

This miliary pattern may also be seen in sarcoidosis, pneumoconiosis, disseminated carcinomatosis, fungal and viral infection. Miliary calcification is extremely rare in miliary tuberculosis. Other causes are to be considered such as histoplasmosis, coccidioidomycosis, schistosomiasis and paragonimiasis.

6. Tuberculous Bronchiectasis

In endobronchial TB, the bronchi are affected in several different ways: a) exogenous lymph node compression; b) intrinsic granuloma formation c) bronchiectasis

Bronchographic evidence of distortion and dilatation of the bronchial tree (bronchiectasis) may develop when the bronchial wall is infected. Healing by fibrosis and cicatrisation leads to irreversible dilatation. Obstruction of a segmental bronchus from compression by enlarged lymph nodes or by bronchostenosis can lead to destructive pneumonitis and subsequent bronchiectasis.

Bronchiectasis is twice more frequent in patients with hemoptysis. This may be asymptomatic and suggested only by non-resolving radiographic shadows despite adequate treatment. A definitive diagnosis of bronchiectasis is made with bronchography, CT scan and bronchoscopy.

7. Tuberculous Bronchostenosis

Tuberculous bronchitis may occur in the absence of a demonstrable x-ray abnormality. If left untreated cicatricial bronchostenosis is almost inevitable with its resultant obstructive atelectasis, pneumonitis and bronchiectasis. Persistent respiratory wheeze may suggest the diagnosis.

8. Tuberculoma

Tuberculomas are round or oval lesions situated most commonly in an upper lobe, the right more than the left ranging from 0.5 to 4 cm or more in diameter. Typically,
they are smooth and sharply circumscribed while up to a fourth may be smooth and lobulated. Small discrete shadows in the immediate vicinity of the main lesion (satellite lesions) may be identified. There may be irregular thickening of the wall of the draining bronchus and in some, actual bronchostenosis.

The majority of these lesions remain unstable and may calcify. The larger the lesion, the more active it is.

B. Extrapulmonary Tuberculosis

Diagnosis of extrapulmonary TB is often difficult. Although a positive chest radiographic findings or a positive tuberculin skin test supports the diagnosis, negative results do not exclude extrapulmonary tuberculosis.

1. Musculoskeletal Tuberculosis

Spinal TB (Pott's Disease)

The disease process most often begins in the anterior part of the vertebral body adjacent to the end plate. Collapse of a vertebral body, particularly the anterior segment, may result in tuberculous kyphosis. Paraspinal infection may involve the psoas muscle, resulting in psoas abscess, which can extend into the groin and thigh. Calcification within the abscess is virtually pathognomonic of tuberculosis.

Many disease processes including metastatic disease and low grade pyogenic infections such as brucellosis, fungal infections and sarcoidosis have imaging findings similar to those of spinal tuberculosis. However, the diagnosis of tuberculosis is favored if a large calcified, paravertebral mass and absence of sclerosis or new bone formation are noted. Conversely, intervertebral disk destruction is more characteristic of a pyogenic infection.

TB Arthritis

TB of the joints is characteristically a monoarticular disease. The triad of juxtaarticular osteopenosis, peripherally located osseous erosions, and gradual narrowing of the interosseous space is termed the PHEMISTER triad and is characteristic of TB arthritis. Relative preservation of the joint space is highly suggestive of tuberculous arthritis; early loss of articular space is more typical of rheumatoid arthritis.

2. Central Nervous System Tuberculosis

CNS tuberculosis may take a variety of forms, including meningitis, tuberculoma, abscess, cerebritis and miliary TB.

TB Meningitis

Abnormal meningeal enhancement that is typically most pronounced in the basal cisterns may be well seen with both CT and MR imaging. This enhancement of the basal cisterns corresponds to the gelatinous exudate. Communicating hydrocephalus is the most common complication of TB meningitis. Also, ischemic infarcts are commonly seen as a complication of cranial tuberculous meningitis. The majority of the infarct is seen in the basal ganglia and internal capsule and result from vascular compression and occlusion of small perforating vessels.

Tuberculoma

Parenchymal disease can occur with or without meningitis and usually manifests as tuberculomas. These may be solitary but are more commonly multiple. The frontal and parietal lobes are the most commonly affected regions. At CT, tuberculomas appear as rounded or lobulated masses with low or high attenuation. They demonstrate homogenous or ring enhancement and have irregular walls of varying thickness.

3. Abdominal Tuberculosis

Ileocecal involvement is seen in 80-90% of patients with abdominal TB. Thickening of the valve lips or wide gaping of the valve with narrowing of the terminal ileum (the Fleischner sign) has been described as a characteristic of tuberculosis. At CT scan, one half of patients with gastrointestinal TB show circumferential thickening of the cecum and terminal ileum, enlargement of the ileocecal valve and mesenteric lymph-ade-nopathy.

Hepatosplenic TB generally manifests in a micronodular (miliary) or macronodular (tuberculoma) form. On CT scans, numerable tiny, low attenuation foci may be seen. The macronodular form is rare. The spleen probably always is seeded during the initial lymphohematogenous spread. Only rarely are the tubercles numerous enough and large enough to undergo caseation and calcify.

4. Renal Tuberculosis

The earliest urographic abnormality is a "moth-eaten" calix due to erosion. This finding is followed by papillary necrosis. Poor renal function, dilatation of the pelvocalyceal system due to a stricture of the ureteropelvic junction, or destructive dilatation or localized hydrocalycosis related to an infundibular stricture may be seen. Cavitation with the renal parenchyma may be detected as irregular pools of contrast material.

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Diagnostic Tests For Tuberculosis

I. Diagnostic Mycobacteriology
   A. Staining and Microscopy
   B. Mycobacterial Culture
   C. Collection and Transport of Specimens
      1. Sputum
      2. Gastric aspirate
      3. Bronchial washings
      4. Urine
      5. Other body fluids and tissue

II. Histologic Examination

III. Newer Diagnostic Tests
   A. Serodiagnosis and Biochemical Markers
      1. Antibody detection
      2. Antigen detection
   B. DNA Probes
   C. Polymerase Chain Reaction

I. Diagnostic Mycobacteriology

A. Staining and Microscopic Examination
Detection of acid fast bacilli (AFB) in stained smears examined microscopically is the first bacteriologic evidence of the presence of mycobacteria in clinical specimens. It is the easiest, least expensive and most rapid procedure for obtaining preliminary information and provides the physician with a presumptive diagnosis of active tuberculosis. It also gives a quantitative estimation of the number of bacilli on the smear and implies infectiousness of the patient. Studies in adults have demonstrated the high specificity of sputum microscopy ranging from 97.5-99.8%. The major disadvantage of the test is its low sensitivity (51.8-53.1%). It is estimated that the lowest concentration of organisms that can be detected by microscopic examination is $10^4$ bacilli per mL of sputum.

Therefore, culture examination should be done on all specimens regardless of AFB smear results. In a local study by Mendoza and Narciso, sputum AFB smear was compared with mycobacterial culture as the gold standard. The sensitivity was 51.8%, specificity 97.5% computed positive predicted value (PPV) 76.3%, and negative predictive value (NPV) 93.0%.

Methods for selective staining of mycobacteria are the conventional Ziehl-Neelsen or Kinyoun stains and the newer fluorochrome stains such as auramine and rhodamine stains. Both the Ziehl-Neelsen and fluorescent acid fast technique are able to detect positive AFB smears although higher positive yields are reported with the fluorescent stains due to easier detection of the fluorescing yellow-orange bacillus even on low magnification.

B. Mycobacterial Culture
A positive culture for M. tuberculosis from body fluids and tissues confirms the diagnosis of tuberculosis. Culture examinations should be done on all specimens, regardless of AFB smear results. A positive AFB smear may represent either M. tuberculosis or some non-tuberculous mycobacterium. Therefore, an AFB-positive smear is not sufficient evidence for bacteriologic diagnosis of tuberculosis and offers only presumptive diagnosis of tuberculosis.

Mycobacterial culture has a low sensitivity in children where only 40-50% of tuberculous cases are culture-proven. Fortunately, for most children with pulmonary tuberculosis, culture confirmation is not necessary if the epidemiologic, tuberculin skin test and roentgenographic information is compatible with the disease. However, cultures should be obtained from the child if the source case is unknown or has a drug-resistant organism, or if the child is immunocompromised or has extrapulmonary tuberculosis.

Traditional culture methods utilize solid culture media which include the egg-potato-based media (e.g. Lowenstein-Jensen) and the agar-base media (e.g. Middlebrook 7H-10, Middlebrook 7H-11). Incubation of inoculated media in 5-10% carbon dioxide atmosphere enhances the number of positive isolates and the number of culturable colonies. The isolation of organisms utilizing traditional culture methods often require 4-6 weeks and another 2-4 weeks for susceptibility testing.

The BACTEC radiometric system uses liquid media containing fatty acid substrates labeled with carbon-14. As the mycobacteria metabolizes the fatty acids, $^{14}CO_2$ is released and can be measured as a marker of bacterial growth. The BACTEC system yields culture and susceptibility results in as few as 7 to 10 days and is more sensitive than traditional media for cultures of sputum specimens from adults. No formal trials comparing BACTEC with traditional methods of culture of specimens from children have been reported.

C. Collection and Transport of Specimens for
Demonstration of Tubercle Bacilli

Success in isolating mycobacteria from clinical material depends on the manner in which specimens are collected and handled after their collection. Painstaking collection of specimens is essential for diagnosis in children because fewer organisms are present as compared with adults. For optimal results, specimens should be transported to the laboratory and processed as soon as possible after collection. Since mycobacterial disease may occur in almost any site in the body, a variety of clinical materials may be submitted to the laboratory for examination. In children, specimens that may be collected include gastric aspirate, sputum, urine, cerebrospinal fluid, pleural fluid, bronchial washings, pus, bone marrow, and biopsy or resected tissue. Specimens must be collected in clean sterile containers and held under conditions that inhibit the growth of contaminants since most specimens will contain bacteria other than mycobacteria. Certain specimen collection procedures are optimal for \( M. \) \textit{tuberculosis}. All specimens from non-sterile sites must be decontaminated before culture.

1. **Sputum**

For older children who are able to expectorate, a series of three early morning specimens should be collected on different days before start of chemotherapy and sent to the laboratory without delay. The patient should be instructed on how to produce a good specimen. Direct supervision of the patient at least during the first time sputum is collected best. Patients should be informed that sputum is the material brought up from the lungs and that mucus from the nose, throat, or saliva is not a good specimen.

The patient should be placed in a well-ventilated area for the collection of sputum specimen and instructed to follow these steps to obtain a good specimen: (1) clean and thoroughly rinse mouth with water; (2) breath deeply three times; (3) after the third breath, cough hard and try to bring up sputum from deep in the lungs; (4) expectorate the sputum into a sterile container collecting at least one teaspoonful. The collected specimen should then be examined by the microscopist to see that the specimen collected is not just saliva.

For patients who have difficulty producing sputum, aerosol induction for 15 to 30 minutes using hypertonic saline (3-10%) can be used to stimulate sputum production. Patients should be instructed to take several normal breaths of the aerosol mist, inhale deeply, cough hard then expectorate into the specimen container. Although aerosol-induced specimens may appear thin and watery, they should be processed as for sputum specimen.

2. **Gastric Aspirate**

Gastric aspiration may be necessary for infants and children who cannot produce sputum even with aerosol inhalation. About 5-10 mL of gastric contents should be aspirated early in the morning after the patient has fasted for at least 8-10 hours, preferably before the child rises and peristalsis empties the stomach of respiratory secretions swallowed overnight. No more than 50-70 mL of sterile water (not saline) should be injected through the stomach tube and the aspirate added to the first collection. Concentration and culture should be performed as soon as possible after collection. If culture cannot be performed immediately, gastric acidity should be neutralized, either with 10% sodium carbonate added by dropper to a pH of 7 as indicated by phenol red or with 40% anhydrous sodium phosphate to green with bromothymol blue as indicated. For these reasons, gastric aspiration is best performed in hospitalized patients.

Three consecutive morning gastric aspirates yield \( M. \) \textit{tuberculosis} in only 30-50% of children and 70% of infants with pulmonary tuberculosis. The yield from random outpatient gastric aspirate samples is exceedingly low.

"The main difficulty in recovering the causative organism is that in primary infection the majority of the cases do not have sputum. Moreover, the bacillary population is not only small but the bacilli are deprived of a bronchial outlet and cannot be recovered since they are trapped within the tissues of the lung and lymph nodes. Another difficulty...is that the younger the child, the more futile are the attempts to obtain sputum specimens... Hence, examination of the gastric contents is a far more useful diagnostic method in younger children." As a rule in the progressive forms of primary infection, notably, tuberculous bronchopneumonia and caseous pneumonia, efforts to recover tubercle bacilli are successful." M Pardo de Tavera (1975)

3. **Bronchial Washings**

Bronchoscopy can be done if the patient cannot cough up sputum spontaneously or if sputum induction and gastric aspiration are not successful. Bronchial washings, brushings, and biopsy specimens may be obtained depending on the diagnostic possibilities and findings. Sputum produced after bronchoscopy should also be collected and examined. In one study, the yield of \( M. \) \textit{tuberculosis} from bronchoscopy specimens has been lower than from properly obtained gastric aspirates.

4. **Urine**

First morning-voided midstream specimen is preferred. Multiple specimens are recommended to demonstrate the presence of mycobacteria.

5. **Other Body Fluids and Tissues**
When non-invasive techniques have not provided a diagnosis, tissue or other body fluids should be obtained for histologic evaluation and culture. Tissue specimens for culture of *M. tuberculosis* should be placed in saline solution (not in formalin) and should be delivered to the laboratory promptly. Alternatively, lymph node aspirates and bits of biopsy tissue can also be inoculated directly into a fluid medium such as Middlebrook 7H9. In-patients with hematogenous of disseminated disease, bone marrow biopsy, lung biopsy and liver biopsy for histologic examination must be considered.

**II. Histologic Examination**

Biopsy of a node, skin lesion, bone or pleura may permit a quick presumptive diagnosis as well as yield specimens for bacteriologic examination. The classic pathologic lesion in tuberculosis consists of caseating granulomas, which may demonstrate acid fast bacilli.

The pathologic events in the initial tuberculous infection depend upon the balance among the mycobacterial antigen load, cell-mediated immunity which enhances intracellular killing, and tissue hypersensitivity which promotes extracellular killing. When the antigen load is small and the degree of tissue sensitivity is high, granuloma formation results from the organization of lymphocytes, macrophages, Langerhans giant cells, and fibroblasts. When both antigen load and the degree of hypersensitivity are high, granuloma formation is less organized. Tissue necrosis in tuberculosis is incomplete, resulting in solid or semisolid acellular and amorphous material referred to as caseous because of its cheesy consistency. When the degree of tissue sensitivity is low, as is often the case in infants or immuno-compromised individuals, the reaction is diffuse and the infection is not well controlled, leading to dissemination and local tissue destruction. Tissue necrosis factor and other cytokines released by specific lymphocytes promote cellular destruction and tissue damage in susceptible individuals.

**III. Newer Diagnostic Tests**

Current techniques for the diagnosis of tuberculosis are beset by a number of limitations and problems. Bacteriologic diagnosis of active tuberculosis in children is often difficult and diagnosis must rely largely on clinical and x-ray examinations which have low specificity and may produce a high proportion of false positive results. Due to the difficulties in establishing the diagnosis of tuberculosis in the pediatric population, there has been considerable interest in the development of rapid diagnostic tests that might be useful in children.

**A. Serodiagnosis and Biochemical Markers**

Immunosassays may involve either detection of antibodies against the TB bacilli or detection of the tuberculous antigen. A variety of mycobacterial antigens such as complex antigens from Bacillus Calmette-Guerin (BCG) and tubercle bacilli or purified glycolipids and proteins from *M. tuberculosis* have been evaluated by means of the enzyme-linked immunosorbent assay (ELISA) method for their diagnostic potential in tuberculosis.

1. **Antibody Detection**

Several studies have used the enzyme-linked immunosorbent assay (ELISA) to detect antibodies to various purified or complex antigens of *M. tuberculosis*. Sensitivity of these tests would depend on the prevalence of tuberculosis in the area, the sensitivity being higher in highly prevalent areas. Specificity on the other hand will depend on the antigen used. Mycobacterial sonicates and autoclaved suspensions of *M. tuberculosis* were examples of crude bacillary antigens used. In adults, the specificity of these tests were shown to range from 49-92% and specificity between 84-98%. Utilizing an adsorbed mycobacterial sonicate in an enzyme-linked immunosorbent assay on samples from 21 children with clinical tuberculosis, Rosen found the TB ELISA to have sensitivity of 25.8% and a specificity of 39.5%.

The low specificity of the ELISA test was attributed to the recent BCG vaccination in children under 5 years of age. Barrera, et al used an ELISA which detects antibody to purified protein derivative and found a sensitivity of 51% for culture-positive pulmonary tuberculosis in children but the sensitivity was only 28% for the clinical cases. Hussey, et al used an autoclaved suspension of *M. tuberculosis* to detect antibodies in serum from 132 children with clinical pulmonary tuberculosis; the test was 62% sensitive and 98% specific. Higher sensitivity was obtained among patients with positive culture results (69%), miliary TB (100%), TB meningitis (80%) and pleural effusion (78%). In contrast to the study by Barrera, there was no correlation as observed with the tuberculin skin test result, BCG vaccination, or nutritional status. However, duration of therapy, increasing age and chronicity of infection were positively correlated.

Development of highly purified antigens such as antigen 5, antigen 6, and antigen A60 have been shown to have improved specificity and improved its potential applicability in serodiagnosis. A small study in Argentina of 21 children with bacteriology confirmed tuberculosis showed that ELISA utilizing antigen 5 yielded a sensitivity of 86% and a specificity of 100%. In children with tuberculous meningitis, ELISA using antigen 5 detected immunoglobulin G (IgG) antibody in the CSF...
in fewer than 20% of cases.\textsuperscript{15} Delacourt, et al used an ELISA to detect IgG and IgM antibodies directed against mycobacterial antigen A60 in children with tuberculosis. At a predetermined specificity of 98%, IgG was detected in 68% of children with clinical disease when results were highly controlled for age and prior BCG vaccination; IgM detection had only 19% sensitivity.\textsuperscript{28} Using the same antigen A60 ELISA at a defined specificity of 95%, Turneer, et al found IgG sensitivity to be only 26% for past tuberculosis, 6% for asymptomatic primary tuberculosis, 14% for symptomatic tuberculosis, and 9% for nontuberculous mycobacterial adenitis.\textsuperscript{21}

2. Antigen Detection

Other investigations have attempted to detect structural components of mycobacteria directly, such as tubercu-losearic acid in sputum, serum, and CSF. These tests yielded high sensitivity and specificity in various clini-cal specimens from adults with tuberculosis.\textsuperscript{22,23,24,25,26} However, these have not been evaluated in a systematic fashion in children. Measurement of tuberculo-losearic acid, a mycobacterial mycolic acid has been used to detect \textit{M. tuberculosis} in clinical specimens. Sada and colleagues established ELISA for detection of mycobacterial antigen in CSF. Among patients diagnosed to have TB meningitis, the test was shown to have a sensitivity of 81% and a specificity of 100%.\textsuperscript{27} Brooks demonstrated a sensitivity of 95% and specificity of 91% when a chromatographic profile of carboxylic acids and detection of tuberculo-losearic were combined and compared with culture results in adults with pulmonary tuberculosis.\textsuperscript{28}

Wadee and coworkers utilized double-antibody sand-wich ELISA to detect \textit{M. tuberculosis} antigens in CSF, pleural and ascitic fluids of diagnosed tuberculous patients.\textsuperscript{28} In this report, ELISA demonstrated specifici-ties of 96% for CSF, 96.7% for pleural fluid and 97.1% for ascitic fluids. Sensitivity was 100% for all three body fluids. In a later report, Chanteau utilized a 45/47 kilodalton antigen immunocapture ELISA test on sputum specimens and demonstrated that the specificity of the test was 95.6%, the sensitivity was less than 40%.\textsuperscript{29} Due to variable sensitivity and specificity results, these tests cannot be recommended for the routine diagnosis of tuberculosis. In addition, these techniques require use of complex techniques such as gas chromatography, mass spectrometry with ion monitoring and expertise which are not commonly available. Moreover, their sensitivity and specificity in children are completely unknown.

Overall, no available serodiagnostic tests for TB has adequate sensitivity, specificity or reproducibility under various clinical conditions to be useful for diagnosis of TB in children. The search for new diagnostic techniques which could be faster, more sensitive and specific than the current microscopic technique and mycobacterial culture is still ongoing.

B. DNA Probes

The tubercle bacillus had specific ribosomal RNA sequences which can be detected in clinical specimens after suitable preparation, by hybridization with specific complementary DNA probes. Radiolabeled DNA is added to a preparation containing the mycobacterial DNA. After hybridization occurs, unlabeled RNA and DNA are washed away, and the amount of hybridiza-tion is measured in a gamma counter. Two types of probes are available: direct and indirect probes. Direct probes are those used directly on samples from patients. Indirect probes are those used on colonies or mycobacteria isolated on solid media from body fluids or tissue. These probes are used to identify the species of mycobacteria grown in pure culture. Roberts utilized whole chromosomal DNA probes in dot blot assays to identify clinical isolates of \textit{M. tuberculosis}, \textit{Mycobacterium avium} complex and \textit{M. gordonae}. This test was able to correctly identify 93% of the mycobacterial cultures grown on agar plates.\textsuperscript{30} In another study, Ellner combined radiometric meth-odology (BACTEC 12B) and probe technology for recovery and identification of mycobacteria.\textsuperscript{31} This procedure resulted in a 5 to 7 week reduction in the average time to final report. However, this method is also labor-intensive.

C. Polymerase Chain Reaction (PCR)

PCR is a technique of DNA amplification that uses specific DNA sequences as markers for microorganisms. In theory, this technique can detect a single organism in a specimen such as sputum, gastric aspirate, pleural fluid, cerebrospinal fluid, or blood. Recent publications show that various PCR techniques, mostly using the mycobacterial insertion element IS6110 as the DNA marker for \textit{M. tuberculosis}-complex organisms, have a sensitivity and specificity greater than 90% for detecting pulmonary tuberculosis in adults.\textsuperscript{32} Use of PCR for detecting \textit{M. tuberculosis} has not been evaluated as extensively in children. Pierre, et al used an IS6110-based PCR to detect \textit{M. tuberculosis} in gastric aspirate samples from 22 children with pulmonary TB.\textsuperscript{33} They found that 15(25%) of 59 samples were positive; however, testing multiple samples or testing samples at least twice improved the sensitivity. When three samples from the same patient were tested two times each, two or more positive results were obtained from 9 of 15 children with TB, but from 0 of 17 controls. However, 2 of 65 single samples from controls were positive by PCR. Using an IS6110-based PCR assay, Starkie, et al tested gastric aspirates from 35 hospitalized children with pulmonary TB and 30 controls to detect \textit{M. tuber-
In a local study, Montoya and co-workers in clinical samples of PCR performance in such children are lacking. With pulmonary disease, although published reports with smear negative but bacteriologically-confirmed tuberculosis. A negative PCR result never eliminated TB as a diagnostic possibility, and a positive result does not confirm it. Performing PCR on gastric aspirates will not distinguish between TB infection and disease that should not be used for children with normal chest radiographs. The high cost of the test, its labor intensity and problems in specificity preclude its use as part of the routine initial evaluation of patients suspected to have tuberculosis. Until advances in PCR technique improve sensitivity and specificity, PCR alone is insufficient as a single diagnostic test for tuberculosis in children. The major use of PCR in children is when the diagnosis of active tuberculosis is difficult and need to be confirmed rapidly to exclude other diagnosis especially in cases of negative AFB smears and TB cultures. PCR may be particularly helpful in evaluating immunocompromised children with pulmonary disease, although published reports of PCR performance in such children are lacking. PCR may also aid in establishing the diagnosis in extrapulmonary tuberculosis because these infections are usually paucibacillary.

Reference:


Tuberculin Skin Test

I. Overview

The tuberculin skin test is the most widely used method to determine latent TB infection (LTBI), individuals who are infected with *M. tuberculosis* and who do not have TB disease. The Mantoux test is the standard and recommended method of giving the tuberculins for screening. The test is based on a delayed (cellular) hypersensitivity to certain antigens of the TB organism contained in extracts of culture filtrates known as "tuberculin".1

Tuberculin reactivity provides a general measure of a person's cellular immune responsiveness. The delayed (cellular) hypersensitivity reaction is the classical reaction brought about by the tuberculin injected intracutaneously. A prior infection with the *Mycobacterium tuberculosis* or tuberculoproteins from BCG vaccine results in T-cell sensitization that releases lymphokines at the site of injection. These lympho-kines then induce local vasodilation, edema, fibrin deposition, and recruitment of other inflammatory cells to the area resulting in induration. Features of the reaction include (1) its delayed course, reaching a peak more than 24 hrs after injection of the antigen; (2) its indurated character; and (3) its occasional vesiculation and necrosis. Reaction to the tuberculin starts 5-6 hours after injection, in which maximal induration is noted within 48-72 hours post-injection, and subsides over a period of days.

In most children, tuberculin reaction first appear 3 to 6 weeks, and occasionally up to 3 months, after initial infection2.

II. The Procedure

A. Preparations of PPD (Purified Protein Derivative) for Mantoux Tuberculin Skin Testing:

PPD (purified protein derivative) tuberculin, which is used for most skin testing, is isolated from culture filtrate by protein precipitation.

1. PPD-RT23

The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommend the 2-tuberculin unit (2-TU) PPD-RT23, as the standardized dose for Mantoux tuberculin skin test surveys3. The PPD-RT23 is the most widely used tuberculin skin test in the world3,4. This is equivalent to two-fifths the concentration of antigen determined to be bioequivalent to 5-T.U. of PPD-S, the standard tuberculin preparation. Therefore, a dose of 0.1 mL of 2-TU PPD-RT23 is biologically equivalent to 0.1 mL of 5-TU PPD-S.

2. PPD-S

The American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) in the US, endorse the 5 TU PPD-S as the standard dose for tuberculin skin test in North America. Newly manufactured batches of tuberculin are currently bioassayed, and the 5-TU standard is the amount of material which produces results equal to those produced by 5-TU PPD-S = 0.0001 mg of PPD-S5,6.

Tuberculin units are defined on a weight basis: 1-TU (one-tuberculin unit) equals 0.02 mcg (micrograms) of 0.1 mL of tuberculin PPD-RT23 SSI. The standard test dose of a commercial PPD preparation is defined as the dose of the product that is biologically equivalent to that contained in 5-TU of PPD-S (i.e. it elicits reactions of equivalent size ±20%)1,5,6. Using a 10-mm cut-off point for positive tuberculin reactivity, a simultaneous comparison study regarding PPD reactivity between 2-TU PPD RT-23 and 5-TU PPD-S involving 202 health workers, was found to be comparable7. The skin test reaction sizes with two antigens (i.e. 2-TU PPD-RT23 and 5-TU PPD-S) did not differ statistically, based on age, sex or prior BCG vaccination. As a rule of thumb, 0.1 mL of the 2 TU of RT23 will have a tuberculin reactivity similar to 0.1 mL of the 5 TU of PPD-S2,3.

B. Administration, Reading and Recording of the Mantoux Tuberculin Skin Test1,3

The Mantoux tuberculin skin test is performed by injecting 0.1 mL of either the 2 TU of PPD RT23 or the 5 TU of PPD-S intradermally into the volar aspect of the forearm, using a gauge 25 to 27 needle tuberculin syringe. A pale wheal 6 to 10 mm in diameter should be evident after injection. The test is then read within 48-72 hours from time of administration.

The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. The diameter of the indurated area, and not the erythema, is measured transversely to the long-axis of the forearm either by palpation or by the ballpoint pen method. The ball point pen technique is done by drawing a straight line from a point of 5 to 10 mm away from both the opposite sides of the margin of skin induration, and continuously drawn towards the center, until a resistance is felt to further movement. The distance between the two opposite points where the resistance is felt is the size of PPD induration, and measured in mm. All reactions should be recorded in millimeters. If no induration is found, "0 mm" should be recorded. Untoward reactions to tuberculin such are uncommon. A
few exquisitely sensitive individuals may have vesicular or ulcerating local reactions to skin testing. Much less encountered are regional adenopathy and fever.

**Note:** Tween 80 is incorporated to the diluent for PPD to reduce adsorption, since PPD is adsorbed in varying amounts by glass and plastics once diluted. To minimize loss of potency due to adsorption, the tuberculin should not be transferred from one container to another. The solution should always be kept cold (+2 degree to +8 degrees Celsius) and protected from light. Aseptic technique should always be observed when aspirating test doses.

**C. Interpretation of the Mantoux Tuberculin Test**

The tuberculin test is a safe and cost-effective test used worldwide as a clinical and epidemiological tool for TB diagnosis and tuberculin surveys, respectively. A reliable interpretation of the tuberculin skin test requires knowledge of the antigen used (tuberculin), the proper technique of the administration and reading of the test, results of epidemiological and clinical experience with the test and conditions that can bring about the false positive and false negative interpretations of the tests.

Factors that may cause false-positive reactions include: nontuberculous mycobacteria and BCG vaccination. False negative reactions may be attributed to anergy, very young age (less than 6 months), recent TB infection or overwhelming TB disease, and live-virus vaccination.

The interpretation of a PPD reaction should be based on the purpose for which the test is given, the prevalence of TB infection in the population being tested, and the consequences of false classification. The likelihood that a person with a positive PPD is actually infected with *M. tuberculosis* is dependent upon the prevalence of tuberculosis in the population group to which the person belongs. This forms the basis for the different cut points used to classify a skin test as positive. The sensitivity and specificity of the tuberculin skin test would depend on the prevalence of TB and Non-tuberculous mycobacteria (NTM) in the area, BCG status and the cut-off point used for defining positive tuberculin reactivity 9,10,11.

Post-BCG tuberculin reactions develop 6-12 weeks after vaccination 9,11. BCG immunization and other Non-Tuberculous mycobacteria (NTM) can bring about tuberculin reactivity. However, the tuberculin reaction believed to be affected by BCG wanes after 5 years from immunization. About 80-90% in children who received BCG as infants have a non-reactive tuberculin skin test at 5 years of age9,10,11. A number of studies have shown that infants, children and adults from countries with intermediate and high tuberculosis rates have the same prevalence of significant tuberculin reactions, regardless of BCG status 12-18.

A positive PPD reaction in individuals residing in areas highly endemic for TB, e.g. 1≥100/100,000 population, is most likely due to exposure from natural infection caused by the *M. tuberculosis*, rather than those caused by BCG immunization for non-tuberculous Mycobacteria (NTM), since most patients who receive BCG vaccination as children, lose their cutaneous hypersensitivity reaction to tuberculin within 5 years 1,2,3. Therefore, a significant reaction more likely represents true exposure to tuberculosis especially in the setting of a recent exposure.

A new TB blood test FDA approved commercially employs a cell-mediated immune response, interferon-gamma that could detect latent TB infection from that caused by BCG vaccine and other non-mycobacterium TB 18. This test however, has yet to be clinically tested in children less than 18 years of age. In children therefore, there is still no reliable method to distinguish tuberculin reactivity, whether from natural infection with TB, from non-mycobacterium TB or from those caused by BCG immunization. Tuberculin skin test reactions using the Mantoux method should be interpreted in the same manner for persons who have received BCG and for those unvaccinated individuals 17. BCG immunization is not a contraindication for tuberculin skin testing.

Approximately 10% of children with culture-proven tuberculosis are Mantoux test negative18,19. Likewise, a negative reaction to tuberculin skin test does not necessarily rule out TB infection. Live-virus vaccines, such as OPV, Varicella, MMR or oral typhoid (TY21a) may cause suppression of the tuberculin reaction. The tuberculin skin test should be administered either on the same day as live virus vaccines or postpone for at least 4-6 weeks 20.

Table 1 gives the factors related to the person being tested, the tuberculin use, the method of administration, error in reading and recording of results that may lead to false negative reactions to the Mantoux test.

**D. Studies to Determine Cut-off Points for Tuberculin Reactivity**

The 1997 National Consensus on Childhood Tuberculosis, proposed two cut-off values for the definition of the positive tuberculin skin test reaction depending on the patient's age and BCG status 21. The ≥10-mm induration size is considered a positive reaction for children less than 5 years of age and for BCG immunized children. Whereas the ≥5 mm induration size is considered the positive cut-off value for children beyond 5 years of age, and for non-BCG vaccinated children. These recommendations were based on the high TB prevalence in
Table 1 Factors that may cause false negative reactions to the Mantoux test

<table>
<thead>
<tr>
<th>1. Factors related to the person being tested</th>
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<tbody>
<tr>
<td>a. Infections: viral - measles, mumps, chicken pox bacterial - typhoid fever, brucellosis, typhus, leprosy, pertussis tuberculosis, pleurisy; fungal - South American blastomycosis</td>
<td>j. complete anergy, giving negative skin test response to PPD as well or other skin test antigens</td>
<td></td>
</tr>
<tr>
<td>b. live attenuated virus vaccinations against measles, mumps, polio, chicken pox</td>
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<td></td>
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<tr>
<td>c. metabolic derangements - e.g. chronic renal failure</td>
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<td></td>
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<tr>
<td>d. nutritional factors - e.g. severe protein depletion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. diseases affecting lymphoid organs such as Hodgkin's disease, lymphoma, chronic lymphocytic leukemia and sarcoidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. corticosteroids and other immunosuppressive agents</td>
<td></td>
<td></td>
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<tr>
<td>g. age: newborns and elderly patients with &quot;waned&quot; sensitivity</td>
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<td></td>
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<tr>
<td>h. incubating or recent, far advanced or overwhelming infection with <em>M. tuberculosis</em></td>
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<td></td>
</tr>
<tr>
<td>i. stresses such as surgery, burns, mental illness, and graft versus host reactions</td>
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</table>

Table 2 shows the results of three local studies that were done to determine the sensitivity and specificity of 5-TU PPD-S among Filipino children using 10 mm induration as cut-off point. Sensitivity ranged from 64.7 to 84.7%; specificity ranged from 54 to 97.7%. All three also showed that BCG and nutritional status do not significantly affect tuberculin reactivity.

While monographs followed by the American Academy of Pediatrics also recommend the ≥10-mm induration cut-off, our pediatric pulmonologists utilize the ≥8-mm induration size as the positive cut-off level in tuberculin reactions. The 1997 National TB Prevalence Survey, advocates the ≥8-mm induration size (using the 2-TU PPD-RT23) as the cut-off size for positive tuberculin reactivity. This concurs with the earlier recommendation of the first National TB Prevalence Survey done locally in 1981-1983, using a lower strength of 1 TU PPD-RT 23. The Center for Tuberculosis in Children, Philippines (CTCP) adheres to the recommendation of the latest National TB prevalence survey utilizing the cut-off point of ≥8-mm induration as the positive size for tuberculin reactivity using 2-TU PPD-RT23 tuberculin.

The Philippines and experiences of other Asian countries, considering the diverse epidemiological conditions prevailing in this region.

Table 2 The sensitivity and specificity of the 5-TU PPD-S among Filipino children

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of Subjects</th>
<th>Age (Range in Years)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolentino &amp; Soriano</td>
<td>166</td>
<td>0 to 5 yrs</td>
<td>64.7%</td>
<td>74.5%</td>
<td>1999</td>
</tr>
<tr>
<td>Bunyi &amp; Soriano</td>
<td>218</td>
<td>7 to 14 yrs</td>
<td>84.7%</td>
<td>54%</td>
<td>1997</td>
</tr>
<tr>
<td>Chan, et. al</td>
<td>270</td>
<td>3 mos to 10 yrs</td>
<td>59.3%</td>
<td>97.7%</td>
<td>1994</td>
</tr>
</tbody>
</table>

Source: The American Thoracic Society
E. Rationale for Cut-off Value for Tuberculin Reactivity

Considerations in the choice for the most appropriate definition of a positive cut-off point for tuberculin reactivity should be weighed judiciously between overdiagnosis and underdiagnosis of TB infection and disease from normal subjects, based on the sensitivity, specificity, and positive predictive value of the test that would depend on clinical and epidemiological factors. The sensitivity of the diagnostic test is the probability that the test result will be positive, while specificity is the probability that the test will be negative. As sensitivity increases, the number of false positive cases increase, leading to a decrease in the specificity.

The positive predictive value (PPV) on the other hand, is the probability that a person with a positive result actually has the disease. It also serves as a crude measure of relative cost-efficiency. That is, it reflects the ratio of the screening program yield (as number of true positives) to the cost of misdiagnosis (as false positives and false negatives) for a given number of screenees. The Mantoux PPD tuberculin skin test is the best screening test for asymptomatic TB patients. In places where TB prevalence of infection is high, the specificity and positive predictive value (PPV) of the PPD tuberculin test are remarkably increased, resulting to a superior tool for screening purposes.

As the prevalence of the disease increase, it becomes more likely that the person being tested actually has the disease with less false positive results. Hence, the more prevalent the disease, the more sensitive the test must be.

A recent study by Chan involving 360 subjects concurred with the 1997 National TB Prevalence Survey showing the ≥8-mm induration as the best cut-off size for positive tuberculin reactivity with a sensitivity of 78.36%, specificity of 89.16%, positive predictive value (PPV) of 96.95%, and accuracy rate of 80.36%. The different cut-off points plotted in the receiver operating characteristics curve (ROC) likewise proved the cut-off value ≥8-mm induration as that best level that could discriminate a positive from a negative Mantoux tuberculin test reaction among children with TB infection and disease.

III. Phenomenon Related to Tuberculin Testing

A. Anergy

The absence of a reaction to the tuberculin skin test does not rule out the diagnosis of TB disease or infection. In immunosuppressed persons, delayed-type hyper-sensitivity responses to tuberculins may decrease or disappear, a condition known as anergy. It may be caused by many factors, such as measles or other viral infections, HIV infection, severe or febrile illness, Hodgkin's disease, sarcoidosis, live-virus vaccination, or the administration of corticosteroids or immunosuppressive drugs. HIV-infected persons may have a compromised ability to react to tuberculin skin tests because of cutaneous anergy.

Anergy is detected by administering at least two other delayed-type hypersensitivity antigens, such as tetanus toxoid, mumps, or Candida, by the Mantoux technique, in conjunction with tuberculin skin testing. Persons who have a reaction of 3 mm or greater than to any of the antigens (including PPD) are not anergic. Individuals who have a positive reaction to tuberculin should be considered infected with M. tuberculosis, regardless of their reaction to other antigens. The results of anergy testing should be recorded in millimeters of induration. In persons demonstrating anergy, the probability of being infected should be assessed, taking into consideration, history of exposure to persons with infectious TB and the high endemicity of prevalence of TB in the area.

B. Boosted Reaction and Two-Step Testing

In some people who are infected with M. tuberculosis, delayed-hypersensitivity to tuberculin may wane over the years. When these people are skin tested many years after infection, they may have a negative reaction. However, this skin test may stimulate (boost) their ability to react to tuberculin, causing a positive reaction to subsequent tests. This boosted reaction may be misinterpreted as a new infection. The booster pheno-menon increases with age and is highest among older persons. Boosted reactions may occur in persons infected with non-tuberculous mycobacteria or in persons who have had a prior BCG vaccination.

Two-step testing is used to reduce the likelihood that a boosted reaction will be misinterpreted as a recent infection and should be used for the initial skin testing of adults who will be retested periodically, such as health care workers. If the reaction to the first test is classified as negative, a second test should be done 1 to 3 weeks later.

A positive reaction to the second test probably represents a boosted reaction (past infection or prior BCG vaccination). On the basis of this second test result, the person should be classified as previously infected and cared for accordingly. This should not be considered a skin test conversion. If the second test result is also negative, the person should be classified as uninfected. In these individuals, a positive reaction to any subsequent test is likely to represent new infection with M. tuberculosis (skin test conversion).

C. Skin Test Conversion

Skin-test conversion is indicative of recent infection
with *M. tuberculosis*, regardless of age. An increase in reaction size of $\geq 10$-mm induration within a period of 2 years for persons with previously negative tuberculosis skin-test reactions, is classified as conversion to positive.

Reference:

3. Statens Serum Institut, Biologicals Division, Facts about the PPD-RT 23 Tuberculin skin test, Denmark.
25. Personal communication with Dr. Fe del Mundo, Founder and President, Center for Tuberculosis in Children, Philippines, 2003.
I. Overview

The diagnosis of childhood tuberculosis is especially difficult compared to that in the adult. It has been referred to as “the missing diagnosis” mainly because of the occurrence of asymptomatic infection and early disease. Moreover, definitive diagnosis by culture of *Mycobacterium tuberculosis* is even more difficult because of its paucibacillary character and the difficulty in collection of specimen. Demonstration of acid-fast bacilli on microscopy and/or tuberculous histologic changes on biopsy provide only presumptive diagnosis in the absence of positive culture. Radiologic examination is often equivocal.

Daniel¹ reviewed the approaches to the diagnosis of mycobacterial disease. Diagnostic tests are based either on recognition of the infecting agent or on recognition of the host response to the agent (see Table 3). For those based on recognition of the infecting agent, there are direct methods that do not employ prior amplification such as direct sputum smear, rapid culture (BACTEC) and tuberculostearic acid detection. Those that employ amplification include sputum smear after short-term culture, ultraviolet microscopy with fluorescence stains, short-term culture with antigen detection by immunobassay, and polymerase chain reaction.

### Table 3. Approaches to the rapid diagnosis of tuberculosis (modified from Daniel¹)

<table>
<thead>
<tr>
<th>I. Recognition of the Infecting Organism</th>
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<tbody>
<tr>
<td><strong>A. Without amplification</strong></td>
<td></td>
</tr>
<tr>
<td>1. Direct (unconcentrated) sputum smear</td>
<td></td>
</tr>
<tr>
<td>a. Light microscopy</td>
<td></td>
</tr>
<tr>
<td>b. Fluorescence microscopy</td>
<td></td>
</tr>
<tr>
<td>2. Rapid culture (BACTEC)</td>
<td></td>
</tr>
<tr>
<td>3. Tuberculostearic acid detection</td>
<td></td>
</tr>
<tr>
<td><strong>B. With amplification</strong></td>
<td></td>
</tr>
<tr>
<td>Sputum smear after short-term culture</td>
<td></td>
</tr>
<tr>
<td>Ultraviolet microscopy with fluorescence stains</td>
<td></td>
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<tr>
<td>Short-term culture with antigen detection by immunobassay</td>
<td></td>
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<tr>
<td>Polymerase chain reaction</td>
<td></td>
</tr>
</tbody>
</table>

### Recognition of host response

Recognition of host response is best illustrated in the tuberculin and BCG tests. Other means include serology and chest radiology. The introduction of ELISA and development of more specific antigens (recognized by monoclonal antibody) have improved serodiagnosis tremendously.

The National Consensus on Childhood Tuberculosis (1997) confirms the ATS statement that a “positive culture with or without a positive smear for *M. tuberculosis* is the gold standard for the diagnosis of TB and must be sought for whenever possible.” In the absence of bacteriologic evidence, however, a child is presumed to have active TB if 3 or more of the following criteria are present as discussed in Radiologic Findings in Tuberculosis:

1. exposure to an adult/adolescent with active TB disease (EPIDEMIOLOGIC)
2. signs and symptoms suggestive of TB (CLINICAL)
3. positive tuberculin (Mantoux) test (IMMUNOLOGIC)
4. abnormal chest radiograph suggestive of TB (RADIOLOGIC)
5. laboratory findings suggestive of TB (histologic, cytological, biochemical, immunological and/or molecular) (LABORATORY)

II. PPS Consensus: Criteria for Diagnosis

1. **Epidemiologic Considerations**

   Every effort must be made to establish a history of exposure to tuberculosis. In a great majority of childhood tuberculosis, the source of infection is the parent, grandparent or caregiver. The Filipino family being an extended one, inquiry must be made on all possible case contacts to include all relatives and close friends who were in contact with the patient.

   The younger the child, the more probable that the source of infection is in the home, among close household contacts. Many older children are infected by outside sources such as teachers, group leaders or young adults. Widespread infection may develop from a single active case at school or a day-care home for children.

2. **Clinical Manifestation**

   Many children with primary tuberculosis are asymptomatic in early disease or may present with minor constitutional manifestations of low grade fever, lassitude, easy fatigability, anorexia, weight loss, malaise and night sweats, which are protein and common to many illnesses.
Physical findings are also nonspecific and localizing symptoms may be absent even in the presence of extensive disease. There are however, clinical findings compatible with tuberculosis such as relatively painless lymphadenitis, meningitis with insidious onset, gibbus, skin granuloma, erythema nodosum, and phlyctenular conjunctivitis. Their presence suggest tuberculous disease and warrant work-up to confirm the diagnosis.

Using lymph node fine needle aspiration in a study of children with cervical lymphadenopathy, Santos found that in those with tuberculous etiology, cervical lymph nodes measuring more than 2 cm numbered at least two, were matted and doughy, and were not accompanied by fever or local inflammatory reaction. In contrast, in those with bacterial (non-mycobacterial) etiology, there were less neck nodes involved, and these were commonly submandibular in location and associated with signs of infection such as fever, leukocytosis, local inflammatory reaction and an apparent focus of infection.

For more detailed discussion, please refer to Clinical Manifestations of Tuberculosis.

3. Immunologic Evidence of Infection

A. Tuberculin Skin Test

The only means of making a diagnosis of tuberculosis infection without disease is through a tuberculin skin test. This test is based on the fact that infection with M. tuberculosis produces sensitivity to certain components of this organism (antigens or specifically, tuberculin). The reaction to intracutaneously injected tuberculin is that of a delayed cellular hypersensitivity.

A significant reaction means that hypersensitivity to mycobacteria has developed, but does not necessarily signify the presence of disease. Clinically, a delayed hypersensitivity reaction to tuberculin is nearly always a manifestation of previous infection with M. tuberculosis or a variety of nontuberculous mycobacteria or a previous BCG vaccination. It can antedate isolation of M. tuberculosis from sputum or other specimens.

Characteristic features of this reaction include: a delayed course, reaching its peak 48-72 hours after the administration of tuberculin; an indurated character largely because of its cellular infiltration; occasionally, vesiculation and necrosis can occur. Interpretation of tuberculin skin test reaction is dictated by the purpose for which the test was given and on the consequences of false classification. A variety of factors - host, antigen used, method of administration, reading and recording - can cause decreased ability to respond to tuberculin or yield a false negative test.

“The tuberculin test is the most important diagnostic tool in tuberculosis, be it recent or remote, active or inactive. In the time-table of tuberculosis it is this biochemical alteration in the tissues of the host that precedes, by a comfortable margin of time ranging from several months to even years the clinical, the bacteriologic and radiologic evidence of the disease.”

M Pardo de Tavera (1975)

(1) Mantoux Test

The current standard for tuberculin skin test is the Mantoux test which is the intradermal administration of 0.1 mL of solution containing 0.1 mcg or 5 TU (tuberculin units) of PPD (purified protein derivative). Data from developed countries estimate the sensitivity and specificity of the test to be about 90% although specificity can vary greatly with the rate of environmental nontuberculous mycobacteria. Locally, it has been shown to have a sensitivity ranging from 19-41% and a specificity of 77-100%. A negative Mantoux test result does not rule out tuberculous infection or disease in a child known to have been exposed to a diseased household contact.

The rationale, principles, technique of administration and interpretation are discussed thoroughly in Tuberculin Skin Test.

(2) Multiple Puncture Test (Tine Test)

This test has been considered by the 1997 National Consensus to be of no value because of inaccuracy and lack of standardization, based on recommendations by the Center for Disease Control, the American Thoracic Society and the American Academy of Pediatrics.

B. Accelerated BCG Reaction or "BCG Test"

An accelerated BCG reaction produces an induration of at least 5 mm 48-72 hours after vaccination, a pustule in 5-7 days, or healing of BCG lesion within 2-3 weeks. Rivera showed the test to have 97% sensitivity and 100% specificity. The diagnosis was established in this study through chest radiographs. In a similar study, de la Pena and Poblete reported a sensitivity of 82% and a specificity of 81%.

The 1997 Philippine Consensus does not recommend the routine use of live attenuated BCG vaccine in the diagnosis of TB in children.

4. Radiologic Findings

There are no pathognomonic radiographic findings in childhood tuberculosis. Neither the presence or absence of the primary disease can be conclusively determined from the chest film alone. Perhaps the only radiographic finding that may be highly suggestive of tuberculosis in infants and children is the uniform stippling of both
lungs found in miliary tuberculosis.

To appreciate the primary complex on chest radiograph, a lateral projection is necessary. With frontal projections alone, the different components of the primary complex may be obscured by the heart and other structures. Partially calcified mediastinal nodes sometimes lie in the midsaggital thoracic plane and may be visible only on lateral films.

A variety of diseases and conditions may be mistaken for tuberculosis. Sarcoidosis and mycotic infections produce shadows in the lung that resemble TB. Tuberculous lobar and lobular consolidations may be indistinguishable from that due to pneumococcal or streptococcal disease.

5. Laboratory Examinations

Laboratory findings suggestive of tuberculosis by diagnostic mycobacteriology, histological, cytological, biochemical, immunological and/or molecular tests are discussed separately in Diagnostic Tests for Tuberculosis.

Reference:
Management of Tuberculosis in Children

I. Principles of Therapy

The successful management of tuberculosis depends upon an understanding of the pathophysiology of the disease. The need for multiple drugs and prolonged duration of therapy is explained by the following characteristics of the causative organism:

1. Naturally occurring drug resistant mutants are present within large bacterial populations even before chemotherapy is started.
2. Mycobacteria replicate slowly, can remain dormant for prolonged periods, and can be eradicated only during replication.
3. Bacilli live in several sites within the host, and each site contains organisms with a different population size, metabolic activity and replication rate.

Controlled clinical trials have thus demonstrated the following principles, on which treatment recommendations are based:

1. Treatment of disease must contain multiple drugs to which the organisms are susceptible.
2. Drugs must be taken regularly.
3. Drug therapy must continue for a sufficient length of time. These therapeutic principles are valid regardless of the age of the patient.

However, several characteristics unique to children need to be considered in their treatment:

1. The pharmacokinetics of various antituberculous drugs are different in children.
2. Children generally have fewer mycobacterial organisms and are thus less likely to develop secondary drug resistance.
3. Extrapulmonary disease is more common in children; medications used must therefore penetrate specific body sites and tissues.
4. Children tolerate higher doses of antituberculous medications per kilogram of body weight with fewer side effects.
5. There may be a need to modify medications to a form that children can tolerate, which can cause problems with stability, bioavailability and compliance.

Present treatment regimens consist of multiple drugs given simultaneously. Since mutant organisms naturally resistant to multiple drugs are extremely rare, this strategy decreases the likelihood of selecting out drug-resistant organisms and prevents the emergence of resistance. An initial intensive phase (consisting of more than two drugs) promotes efficient killing of actively dividing organisms and leads to the rapid reduction of large bacillary populations. A longer continuation phase (using fewer drugs) then follows, which kills slowly or irregularly dividing bacilli, sterilizes lesions and prevents relapse.

Adherence to therapy is still the major issue determining the effectiveness of drug treatment. Several strategies have thus been explored to decrease treatment costs and promote patient compliance. In both adults and children, numerous trials have proven the efficacy of short-course, 6-month chemotherapy for drug-susceptible pulmonary tuberculosis. Efforts to shorten the duration of therapy to even fewer than 6 months, however, have been associated with significant relapse rates. Intermittent, twice- or thrice-weekly administration of drugs has been shown to be as effective and safe as a daily schedule. What is to be the most cost-effective strategy, however, is directly-observed treatment (DOTS).

Table 4 shows the initial empiric therapy of TB in infants, children and adolescents.

Treatment “can only be successful within the framework of overall clinical and social management of patients and their contacts; the ultimate elimination of tuberculosis requires an organized and smoothly functioning network of primary and referral services based on cooperation between the private and public sectors of medical care.”

II. Chemotherapy

Anti-tuberculosis drugs have traditionally been classified as first-line drugs, with superior efficacy and acceptable toxicity or second-line drugs, having either less efficacy, greater toxicity or both. Isoniazid (INH), rifampicin, pyrazinamide (PZA), streptomycin, and ethambutol are all classified as first-line drugs: except for ethambutol, these are all bactericidal agents. A special concern for the pediatric age group is the bioavailability of suspensions used for therapy, which can have a significant impact on patient response.

Table 5 lists the essential antituberculosis drugs including details on the mechanisms of action, dosing, and adverse effects associated with these agents.

Ethionamide, prothionamide, cycloserine, kanamycin, capreomycin, thiacetazone and para-aminosalicylic acid (PAS) are classified as second-line agents, and are used as alternatives when there is either resistance or hypersensitivity to first-line drugs. Unfortunately, none of these drugs are locally available.

Quinolones are also classified as second-line agents and have been demonstrated to be bactericidal against TB bacilli. Ciprofloxacin, ofloxacin and sparfloxacin are among the most studied of the quinolones, which are presumed to act by inhibition of DNA gyrase. Because...
### Table 4 Initial Empiric Therapy in Infants, Children and Adolescents

<table>
<thead>
<tr>
<th>Category</th>
<th>Regimen</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I TB exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• &lt; 5 years</td>
<td>3 months INH</td>
<td>• Immediate prophylaxis controversial for those &gt;5 years, but is recommended by some experts specially if with risk factors e.g. malnutrition, immunocompromised states</td>
</tr>
<tr>
<td>• 3-5 years</td>
<td></td>
<td>• For both groups, re-evaluate and classify as infection/disease after 3 months and revise treatment accordingly</td>
</tr>
<tr>
<td><strong>Class II TB infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PPD conversion within past 1-2 years, (-) CXR</td>
<td>9 months INH</td>
<td>• In the presence of primary INH resistance, use rifampicin</td>
</tr>
<tr>
<td>• PPD (+) not due to BCG, (-) CXR, (-) previous treatment</td>
<td>9 months INH</td>
<td></td>
</tr>
<tr>
<td>• PPD (+) with stable / healed lesion, (-) previous treatment</td>
<td>9 months INH</td>
<td></td>
</tr>
<tr>
<td>• PPD (+) with stable / healed lesion, (+) previous treatment, at risk of reactivation due to: (a) Measles, pertussis, etc (b) Conditions / drugs inducing immunosuppression (IDDM, leukemia, chronic dialysis)</td>
<td>1-2 months For the duration of immunosuppression</td>
<td>12 months INH</td>
</tr>
<tr>
<td>• HIV infection / persons at risk for infection but HIV status unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Class III TB Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pulmonary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Fully susceptible: based on culture results of index case, (-) previous treatment, &lt;10% local prevalence of primary INH resistance</td>
<td>2 months HRZ once daily, followed by 4 months, HR given once daily or as DOT 3x weekly</td>
<td>• Streptomycin preferred in children &lt; 6 years of age, where visual acuity / color perception cannot be monitored reliably</td>
</tr>
<tr>
<td>(b) Susceptibility unknown or initial drug resistance suspected because of big bacillary population, previous treatment (3-1 month), close contact with resistant source case, residence in area with 10% primary INH resistance</td>
<td>2 months HRZ plus E or S once daily, followed by 4 months HR + E / S given once daily or as DOT 3x weekly</td>
<td>• In immunocompromised patients, continuation phase extended to 7 months (total duration of therapy: 9 months) or for at least 6 months after sputum conversion (if applicable), whichever is longer. If susceptibility results unavailable, continue E / S for the entire duration of therapy</td>
</tr>
<tr>
<td>• Extrapulmonary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Severe, life-threatening disease: disseminated/miliary, meningitis, bone/ joint disease</td>
<td>2 months HRZ + E or S followed by 10 months HR + E / S given once daily or as DOT 3x weekly Same regimen as pulmonary disease</td>
<td>• Corticosteroids (usually prednisone at 1 mkday for 6-8 weeks with gradual tapering) beneficial for the following: meningitis, pericarditis, pleuritis, endo-</td>
</tr>
<tr>
<td>(b) Other pulmonary sites</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See Algorithm for Preventive Therapy of Childhood Tuberculosis*

**Philippine Pediatric Society, Pediatric Infectious Disease Society of the Philippines, Philippine Coalition Against Tuberculosis, National Consensus on Childhood Tuberculosis, 1997.**
### Table 5. Essential Antituberculosis Drug^10,11,12^  

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dose (mg/kg)</th>
<th>Adverse Reactions</th>
<th>Other Comments</th>
</tr>
</thead>
</table>
| **INH**    | • Bactericidal agent  
  • Acts on extra- and intra-cellular bacillary populations  
  • Presumed to inhibit biosynthesis of mycolic acid (cell wall component) and affects glycolysis, nucleic acid synthesis | 5-10 max 300 mg/12 yrs 5 max 300 mg >12 yrs 20-40 max 900 mg/12 yrs 15 max 900 mg >12 yrs | • Peripheral neuropathy: pyridoxine supplementation (10 mg daily) if with seizure disorders, diabetes or malnutrition  
  • Other neurological disturbance: optic neuritis, toxic psychosis, generalized convulsions: less common  
  • Systemic or cutaneous hypersensitivity reactions during the first weeks of treatment  
  • Hepatotoxicity: may need to discontinue INH if with symptoms of hepatitis or if transaminase levels increase >3-5x from upper limits of normal | • Rapidly absorbed orally or parenterally  
  • Diffuses well into all fluids/tissues  
  • Absorption decreased by aluminum hydroxide  
  • Increases plasma concentrations of phenytoin, carbamazepine  
  • Routine monitoring of transaminases not believed to be necessary in children  
  • Protect drug from light |
| **Rifampicin** | • Bactericidal agent  
  • Acts on extra- and intra-cellular bacillary populations  
  • Inhibits nucleic acid synthesis | 10-15 max 600 mg/12 yrs 10 max 600 mg >12 yrs 10 max 600 mg >12 yrs | • Gastrointestinal intolerance: may be severe  
  • If intermittent administration: rash, fever, thrombocytopenia, flu-like symptoms  
  • Increased risk of hepatotoxicity if used with INH; recommend INH at 5-10 mg/kg/day and rifampicin 10-15 mg/kg/day when given together | • Rapidly absorbed from the GIT in the fasting state  
  • Diffuses well into all fluids/tissues  
  • May produce reddish coloration of urine, tears, saliva, sputum  
  • Induces hepatic enzymes: may increase dose requirements of corticosteroids, contraceptives, oral hypoglycemics, oral anticoagulants, dapsone, phenytoin, digitalis glycosides  
  • Resistance rapidly develops: must always be used with other anti-TB drugs  
  • Protect drug from light |
| **Pyrazinamide** | • Weakly bactericidal but with potent sterilizing activity within macrophages, areas of acute inflammation | 15-30 max 2g/12 yrs 50-70 max 4 g >12 yrs | • Hypersensitivity reactions: rare  
  • Moderate rises in transaminase levels common in early phase of treatment; may normalize even if drug is continued  
  • Hyperuricemia; occasional reports of gout  
  • Arthralgia, particularly of shoulders | • Readily absorbed from GIT  
  • Rapidly distributed to all fluids/tissues  
  • Monitor glucose levels carefully if patient is diabetic  
  • Protect drug from light |
| **Streptomycin** | • Bactericidal  
  • Acts on extra- and intra-cellular bacillary populations  
  • Presumed to inhibit biosynthesis of mycolic acid (cell wall component) | 20-30 max 1 g/12 yrs 15 max 1 g >12 yrs 25-30 If 2x/wk: max 1.5 g If 3x/wk: max 1 g | • Sterile abscess  
  • Vestibular, auditory function impairment  
  • Hemolytic anemia, lupoid reactions: rare | • Diffuses well into extracellular compartment of most body tissues, tuberculous cavities; little enters CSF  
  • Do not give together with other nephrotoxic, ototoxic drugs  
  • Monitor renal function and reduce dose by 50%, if dec-reased urine output, (+) casts/albumin in urine  
  • Oral dose: 80% absorbed  
  • Dose reduction recommended if with renal disease  
  • Should not be given to children 6 years because cannot reliably monitor visual acuity |
| | | | | |
of concerns about toxicity, their use is limited in children and are included mainly in regimens for multi-drug resistant tuberculosis.

III. Preventive Therapy

Prophylaxis aims to prevent the development of infection among contacts exposed to active disease (primary prophylaxis), as well as to prevent progression to disease among those already infected (secondary prophylaxis). Primary prophylaxis is recommended for children under 5 years or among those with other risk factors for rapid development of disease, since disease may set in even before conversion of the tuberculin skin test. On the other hand, several well-controlled studies have demonstrated the favorable effect of INH on reduction of complications due to lymphohematogenous and pulmonary spread after infection. The protective effect of INH in the latter situation has been shown to last from 19 to 30 years.

The Algorithm for Preventive Therapy of Childhood Tuberculosis illustrates the approach to prophylaxis as proposed in the 1997 National Consensus on Childhood Tuberculosis.

“The role of corticosteroids as an adjunct in the management of childhood tuberculosis from the National Consensus on Childhood Tuberculosis, 1997, is summarized in Appendix 2.”

References:
Appendix 1.

WHO DISEASE CLASSIFICATION AND THE NATIONAL TB CONTROL PROGRAM

Confirmation of tuberculosis in children by AFB smear and/or culture is very limited. Diagnosis relies on a set of five (5) criteria adopted by the 1997 National Consensus on Childhood Tuberculosis: positive exposure (epidemiologic), suggestive signs and symptoms (clinical), positive tuberculin test (immunologic), abnormal chest radiograph (radiologic), and suggestive laboratory findings (laboratory). These criteria, discussed in Diagnosis of Tuberculosis in Children, are based on the natural course and spectrum of tuberculosis from exposure to infection to disease. A child is presumed to have active disease if 3 or more of these criteria are present.

I. WHO Provisional Guidelines for Diagnosis of Pulmonary TB in Children

The WHO Guidelines further clarify the diagnostic assessment to strengthen the clinical impression and guide decision-making regarding the need for therapy. Table 4 on page 101 provides the initial empiric therapy in infants, children and adolescents according to the category of Exposure (Class I), Infection (Class II) and Disease (Class III). (See Table 6.)

II. The National Tuberculosis Control Program

Under the National TB Control Program, TB patients, be they new or old cases, are classified according to TB Treatment Category I, II, II, IV with their definition according to diagnostic and therapeutic status and the appropriate therapy (initial and continuation phase) with isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) or streptomycin (S). (See Table 7.)

Table 6. World Health Organization Provisional Guidelines for the Diagnosis of Pulmonary Tuberculosis in Children

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnostic and/or Therapeutic Status of TB Patient</th>
<th>Initial Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Suspect Tuberculosis</td>
<td>1. An ill child with a history of contact with a confirmed case of pulmonary tuberculosis</td>
<td>2 HRZE</td>
<td>4 HR</td>
</tr>
<tr>
<td></td>
<td>2. Any child:</td>
<td>2 HRES/1 HRZE</td>
<td>5 HRE</td>
</tr>
<tr>
<td></td>
<td>2.1 Not regaining normal health after measles or whooping cough</td>
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</tr>
<tr>
<td></td>
<td>2.2 With loss of weight, cough and wheeze not responding to antibiotic therapy for respiratory disease</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>2.3 With painless swelling in a group of superficial nodes</td>
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</tr>
<tr>
<td>B. Probable Tuberculosis</td>
<td>1. Positive (≥ 10 mm) induration on tuberculin testing</td>
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</tr>
<tr>
<td></td>
<td>2. Suggestive appearances on chest radiograph</td>
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<td></td>
<td>3. Suggestive histologic appearance of biopsy material</td>
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<tr>
<td></td>
<td>4. Favorable response to specific antituberculous therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Confirmed Tuberculosis</td>
<td>1. Detection by microscopy or culture of tubercle bacilli from secretions or tissues or,</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2. The identification of the tubercle bacilli</td>
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</tbody>
</table>

Table 7. World Health Organization. Treatment of Tuberculosis. Guidelines for national programmes

<table>
<thead>
<tr>
<th>TB Treatment Category</th>
<th>Diagnostic and/or Therapeutic Status of TB Patient</th>
<th>Initial Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>New smear-positive TB; Smear-negative with extensive parenchymal lesion; New severe extrapulmonary TB</td>
<td>2 HRZE</td>
<td>4 HR</td>
</tr>
<tr>
<td>II</td>
<td>Previously treated smear-positive TB; Relapse; Treatment failure; Treatment after interruption</td>
<td>2 HRES/1 HRZE</td>
<td>5 HRE</td>
</tr>
<tr>
<td>III</td>
<td>New smear-negative pulmonary TB; Less severe extrapulmonary TB</td>
<td>2 HRZ</td>
<td>4 HR</td>
</tr>
<tr>
<td>IV</td>
<td>Chronic cases</td>
<td>Refer to specialized</td>
<td></td>
</tr>
</tbody>
</table>

References:
1. World Health Organization. Provisional guidelines for the diagnosis and classification of the EPI target diseases for primary health care, surveillance and special studies. EPI/GEN/83/4, 1993
Appendix 2

CORTICOSTEROIDS AS ADJUNCT THERAPY IN TUBERCULOSIS

The National Consensus on Childhood Tuberculosis states (the full discussion is reproduced here, thus):

“Corticosteroids are beneficial as an adjunct in the management of complicated childhood tuberculosis especially when the host inflammatory response contributes significantly to tissue damage or impaired function. There is convincing evidence that corticosteroids are useful in addition to the antituberculosis drugs if suppression of inflammatory response is desired as in the following situations:

1. **Tuberculous Meningitis**: There are considerable evidences that point to the beneficial effect of corticosteroids especially in the second and third stages of TB meningitis. Corticosteroids help in reducing vasculitis, inflammation and ultimately intracranial pressure. Lowering the intracranial pressure limits the tissue damage and favors circulation of antituberculous drugs through the brain and meninges. Likewise, it has been proven to have lowered the mortality rates as well as the long term neurologic sequelae among the survivors.

2. **Tuberculous Pericarditis**: Corticosteroids can relieve cardiac tamponade within hours and prevent constriction if given early together with antituberculosis drugs.

3. **Tuberculous Pleuritis**: Corticosteroids hasten the resorption of pleural fluid. Symptomatic relief of respiratory embarrassment as a consequence of mediastinal shift may be dramatic with the use of corticosteroid in conjunction with anti-tuberculosis drugs, although the long term sequelae of pleural thickening may not be altered with or without steroid therapy.

4. **Endobronchial Tuberculosis**: Corticosteroids are most helpful when the enlarged mediastinal and hilar lymph nodes compress on the tracheo-bronchial tree resulting in respiratory distress, localized emphysema and/or collapsed-consolidation lesions. Clinical improvement is observed as early as ten days and radiologic improvement in three weeks if corticosteroids are given together with antituberculosis drugs before the fourth month of illness. However, if caseation is already advanced, corticosteroids will be of little benefit.

5. **Miliary Tuberculosis**: Corticosteroids give significant benefit to patients with miliary tuberculosis wherein the inflammatory response is so severe as to cause alveolo-capillary block with cyanosis.

The most commonly used corticosteroid is prednisone given at a dose of 1 mg/kg/day for six to eight weeks with gradual withdrawal.”

Dexamethasone is also favored by some experts, e.g. among neurologists, but no comparative trials have been published. For other adjunct therapies such as carbonic anhydrase inhibitors, osmotic agents, please refer to standard textbooks of Neurology, Pediatrics or Medicine.

Reference
Drugs Mentioned in the Treatment Guideline

This index lists drugs/drug classifications mentioned in the treatment guideline. Prescribing information of these drugs can be found in PPD reference systems.

**Antituberculosis**

**Ethambutol**
- Am-Europharma
- Ethambutol HCl
- Biogenerics
- Ethambutol
- Odol
- Pharex Ethambutol

**Ethambutol/Isoniazid/ Vit B₆**
- Alveodril/
  - Alveodril Forte
- Ebutol
- EMB Forte
- Etham 500
- Ethambin-INH
- Ethamizid
- Eth 400
- Fevram
- Forbutol
- Norvit
- Pacibutol

**Ethambutol/Isoniazid/ Rifampicin**
- Myrin

**Ethambutol/Rifampicin/ Isoniazid/Pyrazinamide**
- 4D
- Econokit
- Econokit-MDR
- Myrin-P Forte
- Quadtab
- Rimstar 4

**Ethambutol/Rifampicin/ Pyrazinamide/Vitamins**
- Continukit Plus

**Ethambutol/Rifampicin/ Pyrazinamide/Isoniazid/ Vitamins**
- SCC Kit
- Viper

**Isobutol**
- Bisobutol

**Isobutol/Rifampicin/ Pyrazinamide**
- Molecure 1 & 2

**Isoniazid**
- Am-Europharma
- Isoniazid
- Bacciter
- Biogenerics Isoniazid
- Curazid Forte
- Norvit
- Pharex Isoniazid
- UL Isoniazid 400

**Isoniazid/Rifampicin**
- Continupack

**Isoniazid/Vit B₆**
- Comprilex Pediatric Syrup
- Isoxin
- Koccid
- Nicetal
- Norvit Plus
- Odinah
- Therabacule
- Trisofort
- Trisovit
- UL Isoniazid 400

**Isoniazid/Vitamins**
- Trisofort
- Trisovit

**Pyrazinamide**
- Am-Europharma
- Pyrazinamide
- Biogenerics Pyrazinamide
- Drugmaker's Biotech
- Pyrazinamide
- Mycobak
- Pharex Pyrazinamide
- Pyramin
- Pyrasol
- PZA-Ciba
- RiteMED Pyrazinamide
- Zapedia
- Zeure
- Zinaplex

**Rifampicin**
- Am-Europharma
- Rifampicin
- Biogenerics Rifampicin
- Carfamin
- Crisarfarm
- Dipicin
- Drugmaker's Biotech
- Rifampicin
- Fampisec
- Fevram
- Koccifam
- Lypro-cap
- Medifam
- Natricin Forte
- Odifam
- Pharex Rifampicin
- PMI Rifampicin
- Ramcin
- Refam
- Relixan
- Rycin
- Rifadin
- Rifamax
- Rimactane
- Rimaped
- RiteMED
  - Rifampicin
  - Tubercrox

**Rifampicin/Isoniazid**
- Bifix
- Continupack
- Kidz Kit 2
- Rifinah
- Rifzin
- Rimactazid 225/
  - Rimactazid 300/
  - Rimactazid 450/
  - Rimactazid 600

**Rifampicin/Isoniazid/ Ethambutol**
- Combikids
- Combi Pack
- Continokit
- TRES
- Tri-Pack
- Tritab
| Econopack |  
| Econopack-TDR |  
| Kidz Kit 3 |  
| M-O-P/M-O Compliance Pack |  
| Rifater |  
| **Streptomycin** |  
| YSS Streptomycin Sulfate |  
| **Corticosteroids** |  
| **Prednisone** |  
| Drazone |  
| Drugmaker's Biotech Prednisone |  
| GXI Prednisone |  
| Orasone 5/Orasone 20 |  
| Organon Prednisone |  
| Pred 5/10/50 |  
| Roidrenal |  