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Founder-Editor

A Parthasarathy
MD DCH DSc (Hon) FIAP
Senior Consultant Pediatrician, AP Child Care, Chennai
Former Distinguished Professor of Pediatrics
The Tamil Nadu Dr MGR Medical University
Retired Senior Clinical Professor of Pediatrics
Madras Medical College
Institute of Child Health and Hospital for Children
Chennai, Tamil Nadu

Editors-in-Chief

PSN Menon
MD MNANS FIAP
Consultant and Head
Department of Pediatrics
Jaber Al-Ahmed Armed Forces Hospital, Kuwait
Former Professor of Pediatrics
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MKC Nair
MD MMedSc PhD DSc MBA FIAP
Vice-Chancellor
Kerala University of Health Sciences, Thrissur
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Chief Academic Editors

Piyush Gupta
MD FNNF FIAP FAMS
Professor
Department of Pediatrics
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Guru Teg Bahadur Hospital
New Delhi

Ritabrata Kundu
MD FIAP
Professor
Department of Pediatrics
Institute of Child Health
Kolkata, West Bengal

Executive Editor

Alok Gupta
MD FIAP
Pediatrician and Counselor
Pediatric Specialties Clinic, Jaipur
Former Assistant Professor (Pediatrics)
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Academic Editors

Abhay K Shah
MD DPed FIAP
Senior Consultant Pediatrician and Director
Children Hospital
Ahmedabad, Gujarat

Ashok Rai
MD PhD FIAP FIAMS FNNF FACI
Senior Consultant Pediatrician
Surya Superspecialty Hospital, Kilkari Institute of Child Health
Director, Indian Institute of Cerebral Palsy
and Handicapped Children
Varanasi, Uttar Pradesh

Dhanya Dharmapalan
MD PG Dip in PID (Oxford)
Consultant in Pediatrics and Pediatric
Infectious Diseases
Apollo Hospitals
Navi Mumbai, Maharashtra

Jaydeep Choudhury
DNB (Ped) MNAMS FIAP
Associate Professor
Department of Pediatrics
Institute of Child Health
Kolkata, West Bengal

K Nedunchelian
MD (Ped) DCH FIAP
Head (Research and Academics)
Senior Consultant Pediatrician
Mehta Multispecialty Hospitals India Pvt Ltd
Chennai, Tamil Nadu

P Ramachandran
MD (Ped) DNB (Ped)
Professor of Pediatrics and
Associate Dean (PG Studies)
Sri Ramachandra Institute of Higher
Education and Research
Chennai, Tamil Nadu

Ex-Officio Editorial Advisers

Digant D Shastri
MD (Ped) PGDHHM FIAP
Senior Consultant Pediatrician
Killol Children Hospital
Surat, Gujarat
President IAP 2019

Santosh T Soans
MD FIAP
Professor and Head
Chief Neonatal and Pediatric intensive Care Division
AJ Institute of Medical Sciences and Research Centre
Mangaluru, Karnataka
President IAP 2018

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MD DCH FIAP
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Forewords

Digant D Shastri, Santosh T Soans

Contents

SECTION 10   DISEASES OF KIDNEY AND URINARY TRACT   793–856

SECTION 11   DISEASES OF BLOOD   857–948

SECTION 16   RHEUMATOLOGY   1127–1158

SECTION 17   INTENSIVE CARE AND EMERGENCIES   1159–1226

SECTION 18   PEDIATRIC SUBSPECIALTIES   1227–1336

5.25

Tuberculosis

Aparna Mukherjee, Anuj Singh, Rakesh Lodha

INTRODUCTION

Tuberculosis (TB) is one of the most common causes of mortality worldwide. An estimated 6.3 million new cases of TB were seen in 2016, of which 1.3 million died due to TB in 2016. Children represent about 11% of all TB cases. Approximately 67 million children are infected with TB (latent TB) and are therefore at risk of developing disease in the future. Despite the best of efforts, childhood TB is still underreported in most of the countries.

EPIDEMIOLOGY

Incidence of TB cases varies among different populations and regions from under 10 per 100,000 population in most high-income countries to 150–300 in most of the 30 high-burden countries. The World Health Organization (WHO) South-East Asia Region (WHO-SEAR) accounted for 45% of the incident cases. TB is the ninth leading cause of death worldwide; it is the main cause from a single infectious agent. About 82% of TB deaths among human immunodeficiency virus (HIV)-negative people occurred in the WHO African Region and the WHO-SEAR in 2016; these regions accounted for 85% of the combined total of TB deaths in HIV-negative and HIV-positive people. India accounted for 33% of global TB deaths among HIV-negative people, and for 26% of the combined total of TB deaths in HIV-negative and HIV-positive people. As per India TB report 2018, the incidence was 211 per 100,000 and mortality of 32 per 100,000 population.

The incidence of drug-resistant TB has increased over the past few years and is a challenge for the whole world due to diagnostic and therapeutic challenges. In 2016, worldwide estimates for multidrug-resistant (MDR)/rifampicin (RIF)-resistant TB in new, and previously treated cases were 4.1% and 19%, respectively.

PATHOGENESIS

Mycobacterium tuberculosis (MTB) bacilli are acid-fast, nonspore-forming, nonmotile, pleomorphic, weakly gram-positive curved rods 1–5 μm long, typically slender, and slightly bent. They may appear beaded or clumped under microscopy. They are obligate aerobes that grow in synthetic media containing glycerol as the carbon source and ammonium salts as the nitrogen source. Other closely related mycobacteria, such as *Mycobacterium bovis*, *Mycobacterium africanum*, and *Mycobacterium microti*, along with MTB form the MTB complex. The characteristic property is acid-fastness, which is imparted by the ability to form stable mycolate complexes with arylmethane dyes that resist discoloration with ethanol.

The spectrum of affliction by MTB includes exposure, infection, and disease.

- *Exposure* means that the child had significant contact with a person with infectious TB but lacks proof of infection.
- *Infection* occurs when an individual inhales droplets, which contain mycobacteria, which survive intracellularly in lung and lymphoid tissue. In this stage, child is *asymptomatic* and has a normal physical examination.
- *Disease* occurs when the signs or symptoms or radiographic manifestations become apparent.

Not all infected individuals have the same risk of developing disease. An immunocompetent adult with untreated TB infection has approximately a 5–10% lifetime risk of developing disease. In contrast, an infected infant has a 40% chance of developing disease within 9–12 months.

Lung is the portal of entry in majority of cases. Bacilli enter alveolar passage in an aerosol droplet and interact with macrophages or type II pneumocytes and are phagocytosed in a process initiated by bacterial contact with macrophage mannose and/or complement receptors. On entry into a host macrophage, MTB initially resides in an endocytic vacuole called the phagosome. If the normal phagosomal maturation cycle occurs, i.e. phagosome-lysosome fusion, these bacteria may encounter a hostile environment that includes acidic pH, reactive oxygen intermediates, lysosomal enzymes, and toxic peptides. Interferon-gamma (IFN-γ) plays a key role for a protective immune response. IFN-γ, produced mainly by CD4+ (cluster of differentiation), CD8+ T cells, and the natural killer cells, synergizes with tumor necrosis factor-α and activates macrophages to kill intracellular bacilli. Bacteria may evade destruction by preventing phagosome-lysosome fusion and cause macrophage necrosis. These bacilli, which survive within macrophage, are carried to regional lymph nodes. The *primary complex (Ghon complex)* of TB includes

local infection at the portal of entry and the regional lymph nodes that drain the area.

There is tissue reaction at initial foci over next 2–12 weeks; and hypersensitivity develops, which heal by calcification or fibrosis. Occasionally, this portion may continue to enlarge and lead to focal pneumonitis and pleuritis, and if caseation is intense then may lead to cavitation. During the development of the primary complex, tubercle bacilli are carried to most tissues of the body through the blood and lymphatic vessels.

Disseminated TB occurs if host cellular immunity is inadequate. Bacterial replication is more likely to occur in organs with conditions that favor their growth, such as lung apices, brain, kidneys, and bones. The time between initial infection and apparent disease is variable. Pulmonary TB that occurs after 1 year of primary infection is due to endogenous growth of bacilli. This reactivation of TB is rare in children but common in adults and adolescents. Occasionally reinfection can occur in immunocompromised individuals or those living in highly endemic areas.

DIFFERENCES BETWEEN TUBERCULOSIS IN ADULTS AND CHILDREN

Childhood TB is not simply a reflection of the adult spectrum of disease. Characteristics of TB in children include the paucibacillary nature; preponderance of primary focus and lymph node disease; higher chance of dissemination into serious manifestations, such as miliary TB, TB meningitis (TBM), and spinal TB; higher burden of extrapulmonary TB (EPTB); challenges in diagnosis due to inability to expectorate sputum; and difference in pharmacokinetic or pharmacodynamics characteristics of antitubercular drugs.

PULMONARY TUBERCULOSIS

Intrathoracic involvement in children is varied and may include the following:

- *Primary focus:* Primary focus or Ghon focus that results from primary infection is usually a single focus of parenchymal involvement with or without pleural component. The primary focus along with the draining regional lymph node is called the primary or Ghon complex. This may get complicated and result in cavitation or intrabronchial spread.
- *Lymph node disease:* As a result of primary infection, parahilar and paratracheal nodes may be involved; complications may include airway involvement leading to alveolar collapse or pneumonia.
- *Pleural or pericardial effusion:* This represents a hypersensitivity reaction resulting in straw-colored fluid with high lymphocyte count. If mycobacterium bacilli grow in pleural space, localized empyema is formed. Pericardial effusion may lead to constrictive pericarditis.

- *Miliary disease:* This results from hematogenous dissemination of bacilli; < 2 mm nodules are seen on chest X-ray extending up to the periphery.
- *Adult-type cavitory lesion:* This is usually seen around 8–10 years of age and beyond.

Clinical Features

Pulmonary TB can present with cough and/or fever for more than 2 weeks, not responding to a course of antibiotic for 7–10 days; weight loss (more than 5% of the highest recorded weight in the past 3 months) or not gaining weight; poor appetite; lethargy or easy fatigability; and night sweats. There may be history of contact with an open case of TB within the last few years.

Diagnosis

Tuberculin Skin Test (Mantoux Test)

Tuberculin skin test (TST) is an intradermal skin test with 5 TU of purified protein derivative (PPD)-S or 2 TU of PPD RT 23 or equivalent, read after 48–72 hours. An induration of 10 mm or more is considered positive. In immunocompromised individuals, induration of 5 mm or more is considered positive. Positive TST merely indicates presence of tubercular infection and not disease; hence, it can only *aid in diagnosis* of TB disease and not *confirm* it.

Imaging

- *Chest X-ray:* Radiological features highly suggestive of TB include hilar or paratracheal lymph nodes with or without parenchymal involvement, miliary pattern, fibrocavitary lesion. Some examples are given in **Figures 5.25.1 to 5.25.4**. If left untreated, miliary nodules may coalesce and may reach 3–5 mm in size, radiologically, described as a "snow-storm" appearance.
- *Contrast-enhanced computed tomography (CECT) chest:* Computed tomography (CT) chest may be done in cases where the chest X-ray is not conclusive. CECT chest enables evaluation of parenchymal lesion; identification of necrosis in lymph nodes; description of pleural, airway, and diaphragmatic pathologies; and evaluating visualized bones. CECT features suggestive of TB include necrotic lymph node with a low-density center surrounded by rim enhancement (rim sign), 2–4 mm centrilobular nodules, and tree-in-bud appearances (sharply marginated linear branching opacities around terminal and respiratory bronchioles) indicating endobronchial spread, thick-walled cavity surrounded by parenchymal lesion indicating active disease. CT may also be useful in undertaking guided aspiration/biopsy from mediastinal nodes for cyto/histopathology and microbiological diagnosis.
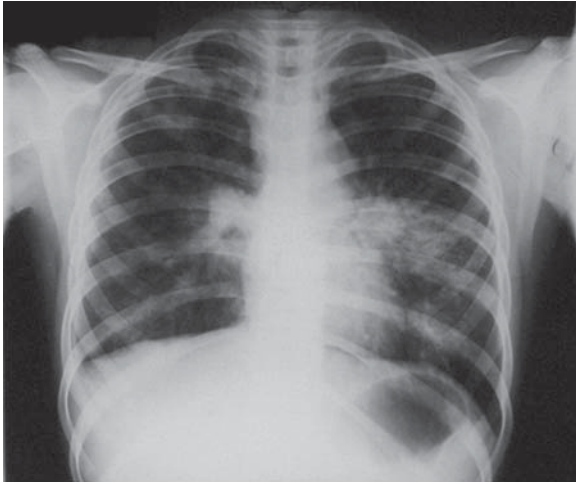
Fig. 5.25.1: Chest X-ray showing bilateral infiltrates.
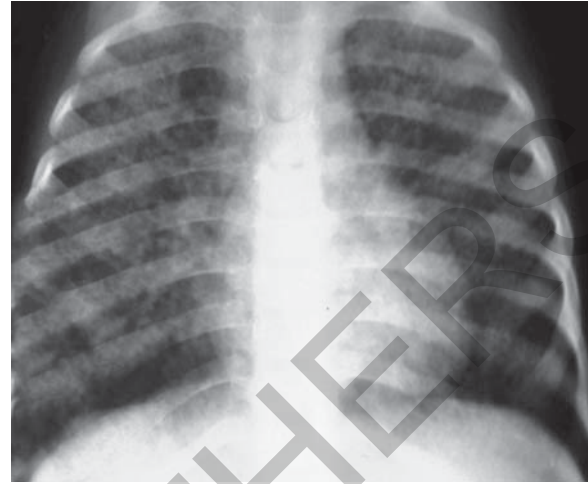
Fig. 5.25.3: Chest X-ray of a 2.5-year-old girl with miliary tuberculosis.
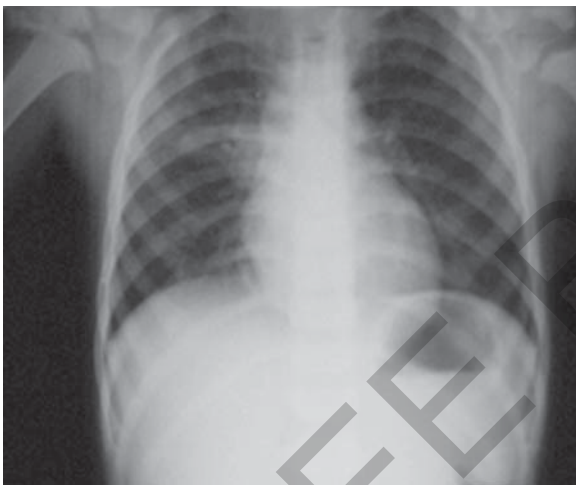
Fig. 5.25.2: Chest X-ray of a 5-year old with collapse consolidation of the right middle lobe.
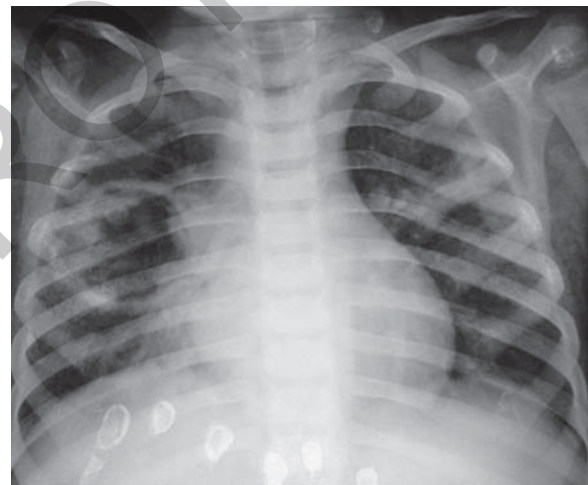
Fig. 5.25.4: Chest X-ray showing a cavitary lesion.

- *Endobronchial ultrasound (EBUS):* EBUS is a newer modality of diagnosis, which is feasible and useful in older children. In case of older children with large hilar or subcarinal lymph nodes, EBUS–transbronchial needle aspiration (TBNA) may be tried to obtain sample for cytological and microbiological diagnosis. Studies have documented a definitive diagnosis of 57% using TBNA in the cases of mediastinal lymphadenopathy in children. However, this is a technique, which is yet to be available widely for diagnosis of TB in children. Moreover, EBUS may reveal a pattern of multiple hyperechoic foci without an acoustic shadow over a hypoechoic background. This is called the "starry sky sign" and is about 51.6% and 100% sensitive and specific, respectively, in the diagnosis of tubercular mediastinal nodes.

- *Magnetic resonance imaging (MRI) chest:* This mode of diagnosis can be employed for follow-up of mediastinal nodal disease instead of CT chest to reduce radiation exposure. The presence of diffusion restriction in lymph nodes along with peripheral enhancement suggests active disease.

Microbiological Confirmation

In spite of the fact that approximately 50% of intrathoracic TB in children is diagnosed clinico-radiologically, every attempt should be made to document a microbiological confirmation in each case.

- *Sample collection:* A major challenge in microbiological diagnosis of childhood TB is the difficulty in obtaining

appropriate sample, as children usually cannot expectorate sputum. Gastric aspirate/lavage and induced sputum are feasible options of collecting respiratory samples even in ambulatory, nonhospitalized children.

- *Examination of smear from respiratory samples under light microscopy after Ziehl–Neelsen (ZN) staining:* It is still the most widely accessible investigation in majority of high-burden areas. In spite of a high specificity, the sensitivity of smear examination remains variable (25–80%).
- *Culture:* Löwenstein–Jensen (LJ) culture media (LJ medium) is the most widely used solid media for the determination of characteristic features of colonial morphology, growth rate, and pigment production. The yield of culture varies from 30% to 50%. Excessively long period required for the isolation of MTB by conventional culture techniques has led to the development of other techniques for culture: BACTEC radiometric assay, Septi-Chek acid-fast bacilli (AFB) system, and mycobacterial growth indicator tube (MGIT) culture. BACTEC–MGIT 960 culture system uses a fluorescent compound embedded in silicone on the bottom of the tube containing modified 7H11 broth with an antibiotic mixture and growth supplements for mycobacteria. As this fluorescent compound is sensitive to oxygen, depletion of the latter by the growth of mycobacteria unmasks the fluorescence, which can be detected by observing the tube under long-wave ultraviolet light. Liquid systems are more sensitive for detecting mycobacteria and may increase the case yield by 10% over solid media as well as reduce time to result from weeks to days. Average time to detection in these systems is 8–14 days, culture being declared negative if no result till 42 days. For drug susceptibility testing, the delay may be reduced to as little as 10 days, compared with 28–42 days with conventional solid media.
- *Microscopic observation drug susceptibility (MODS) assay:* MODS assay is an inexpensive, rapid, and sensitive diagnostic method utilizing manual liquid culture method (Middlebrook 7H9 broth culture) and an inverted light microscope to detect the growth of MTB in the form of "tangles or cords." In a study from Peru, where the assay was developed, MODS detected 94% of 1,908 positive sputum cultures, whereas conventional LJ culture detected only 87%. This assay is not yet available widely and has some problems as it is operator dependent and labor intensive, and more studies in nonresearch settings are needed to validate its use.
- *Nucleic acid amplification test (NAAT):* Polymerase chain reaction (PCR), fully automated platform of real-time PCR, and loop-mediated isothermal amplification (TB-LAMP) platform are the available variations of NAAT. Automated cartridge-based NAAT (CBNAAT), such as Xpert MTB/RIF test, is fully automated real-time PCR-based assay, which not only detects MTB, but also rifampicin (RIF) resistance. WHO as of now strongly recommends that CBNAAT should be used in children, when there is strong suspicion of MDR TB or in the case of HIV–TB coinfection. It may also be used in any case where pulmonary TB is suspected, depending on the available resources. The main advantage of this assay is the rapid turnover time, less chance of human error, and ability to simultaneously detect *MTB* and resistance to RIF. In a meta-analysis published by WHO, the overall pooled sensitivity of Xpert MTB/RIF compared against culture as a reference standard in children presumed to have TB was 66%; the samples used were induced sputum, expectorated sputum, and gastric lavage. The pooled specificity of Xpert MTB/RIF compared against the gold standard, culture was at least 98%. The sensitivity of Xpert MTB/RIF to detect RIF resistance in specimens from children was 86%.
- *Molecular drug resistance testing–Line probe assays:* Line probe assays are strip tests that simultaneously detect MTB bacteria as well as genetic mutations that indicate isoniazid (INH) and/or RIF resistance.

T-cell Based Interferon-gamma Release Assays

Interferon-gamma release assays (IGRA) are in vitro tests of cell-mediated immune response, which are mostly helpful in detecting latent TB infection, not disease. The two commercially available IGRAs are the QuantiFERON-TB (QFT) Gold In-Tube (GIT) assay (Cellestis Ltd, Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Oxford, the United Kingdom). The QFT-GIT assay is an enzyme-linked immunosorbent assay (ELISA)-based whole-blood test that quantitates IFN-γ released in response to antigenic stimulation from three TB-specific peptides, namely, early secreted antigenic target of 6 kDa (ESAT-6), 10-kDa culture filtrate protein (CFP-10), and TB7.7 in a simple in-tube format. T-SPOT.TB is an enzyme-linked immunospot assay designed to measure the number of IFN-γ-producing T-cells in response to ESAT-6 and CFP-10 peptides. The advantage of these assays lies in the fact that they are not affected by previous bacille Calmette–Guérin (BCG) vaccination, do not cross-react with most of the nontubercular mycobacterium (except *Mycobacterium kansasii*, *Mycobacterium szulgai*, and *Mycobacterium marinum*), are not affected by observer bias, and require only one visit for testing. The sensitivity of QFT assay and T-SPOT.TB assay is 75–85% and 90–95%, respectively. The sensitivity is lower in high-incidence regions. The shortcoming of these assays includes the inability to distinguish between latent and active TB and high cost. The immune response leading to the release of IFN-γ is inconsistent in children below 4 years of age; and hence, interpretation of IGRA may be difficult in this age group. The sensitivity of QFT-GIT is variable in children below 4 years of age with higher number of indeterminate results.

Antigen Detection Tests

Lipoarabinomannans (LAMs) are phosphorylated lipopolysaccharides, which are a major cell wall component of bacteria of the genus *Mycobacterium*. Antigen detection assays based on capture ELISA format to detect LAM in urine hold promise as an easy, point-of-care, noninvasive tool for diagnosing active TB. However, the low sensitivity of urinary LAM (17–50%) as compared with the gold standard of culture offsets the advantages. The specificity is acceptable (88–95%). This diagnostic tool may be particularly helpful in the selected subset of patients with HIV/TB coinfection, where the sensitivity increases.

Antibody Detection Tests

There is no role of any serological diagnosis in the form of antibodies against tubercular antigens in the diagnosis of any type of TB—pulmonary or extrapulmonary. Such tests are currently banned by the Government of India.

Flowchart 5.25.1 depicts an algorithm that is used to diagnose intrathoracic TB in children.

Treatment

Category-based treatment is applicable for children with TB as well. Category 1 antitubercular therapy (ATT) is to be started for new cases, which includes 2 months of intensive phase with INH, RIF, pyrazinamide, and ethambutol (HRZE), followed by 4 months of maintenance phase with INH, RIF, and ethambutol (HRE). A 10-month maintenance phase is required for osteoarticular and central nervous system (CNS) TB. **Table 5.25.1** shows the category-based ATT for children.

The medications should preferably be given daily on mg/kg body weight basis. A meta-analysis conducted on

Flowchart 5.25.1: Diagnostic algorithm for childhood intrathoracic tuberculosis.
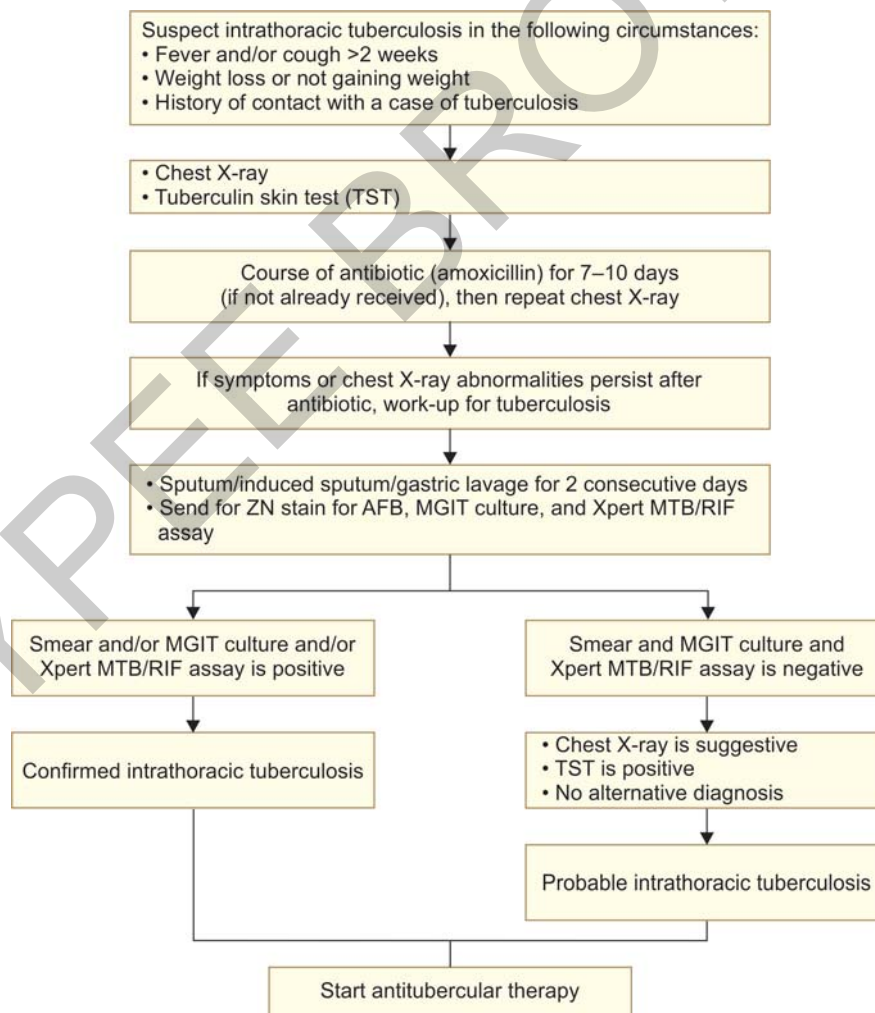
(AFB: acid-fast bacilli; MGIT: mycobacteria growth indicator tube; TST: tuberculin skin test; ZN stain: Ziehl–Neelsen staining)

Table 5.25.1: Category-based treatment for tuberculosis in children.

Category of treatment	Inclusion criteria	Treatment regimen	
		Intensive phase*	Continuation phase
New cases (Category 1)	• New smear-positive pulmonary tuberculosis • New smear-negative pulmonary tuberculosis • New extrapulmonary tuberculosis	2 HRZE	4 HRE[†]
Previously treated cases (Category 2)	• Relapse, failure to respond or treatment after default • Retreatment	2 HRZES + 1 HRZE	5 HRE

Note: The prefix number denotes the number of months.
*Intensive phase can be extended by 1 month in case of unsatisfactory response.
[†]Continuation phase to be extended for 10 months in cases of osteoarticular and central nervous system tuberculosis.
(H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; S: streptomycin)

studies in children showed that intermittent therapy of antitubercular drugs was less likely to cure than daily therapy. **Table 5.25.2** details the recommended daily doses of the four first-line antitubercular drugs according to the latest WHO guidelines. The dose of the antitubercular drugs should be adjusted according to the current weight of the child in each follow-up visit during therapy.

Monitoring

Any child on ATT should be regularly monitored for the following:

- *Response to treatment:* Clinicoradiological improvement at 2 months and 6 months of ATT is assessed by weight gain, symptomatic improvement, and more than two-thirds resolution of radiological abnormalities. If AFB or MGIT is positive at baseline, gastric lavage and induced sputum should be repeated at 2 months for ZN staining and MGIT culture.
- *Adverse events:* Any feature suggestive of hepatitis, rash, and/or peripheral neuropathy should be promptly investigated. The antitubercular drugs should be modified if the child is symptomatic with abdominal pain, vomiting, or yellowish discoloration of sclera and urine; or if the liver enzymes are deranged (aspartate aminotransferase/alanine aminotransferase) more than five times the upper limit; or total bilirubin is raised. INH, RIF, and pyrazinamide should be stopped, and the modified regimen should contain ethambutol and a fluoroquinolone, such as levofloxacin. Injectable streptomycin may be added if the disease severity warrants. Once the symptoms are relieved and liver parameters are normalized, the first-line antitubercular drugs should be restarted sequentially, increasing every 5–7 days after checking the liver functions. Once the full dose of conventional antitubercular drugs is reached, the modified regimen may be stopped.

Role of Corticosteroids in Tuberculosis

Routinely there is no role of corticosteroids in the management of intrathoracic TB in children. However, in the

Table 5.25.2: Daily dose and maximum doses of isoniazid, rifampicin, ethambutol, and pyrazinamide in children.

Drug	Dose (range) mg/kg body weight/day	Maximum dose mg/day
Isoniazid	10 (7–15)	300
Rifampicin	15 (10–20)	600
Ethambutol	20–25	1,500
Pyrazinamide	30–35	2,000

case of superior mediastinal compression syndrome due to mediastinal nodes, oral corticosteroids may be used.

◼ TUBERCULAR LYMPHADENITIS

Lymph node TB is the most common form of EPTB, especially in children. Approximately 35% of EPTB cases are lymph node TB. Deep-seated nodes of the mediastinum (mediastinal TB) or abdomen (abdominal lymph node TB) may also be affected.

A child with lymph node TB presents with matted, usually nontender lymph nodes >2 cm size at one or more sites, not responding to antibiotic treatment and persisting for > 1 month. The child may also have fever, poor appetite, and weight loss/inability to gain weight. The lymph node may become fluctuant and burst forming a sinus or ulcer with undermined edges **(Fig. 5.25.5)**.

Diagnosis

Tuberculin skin test: Positive TST ≥ 10 mm suggests tubercular infection but does not confirm disease. X-ray of chest should be done to evaluate pulmonary involvement.

Fine needle aspiration of the nodes: Antigravity Z technique should be applied for aspiration. Deep-seated nodes can be accessed by ultrasound guidance. Sample should be sent for cytopathology, AFB, MGIT culture, and CBNAAT assay. The cytopathological characteristics of tubercular lymphadenitis

Fig. 5.25.5: Tubercular axillary lymph nodes with overlying ulcer formation.

include epithelioid cell granuloma with or without Langhans cell granuloma with or without necrosis. Staining for AFB is a must in all cases suspected to be lymph node TB.

Excision biopsy: It may be needed if cytopathology from aspiration is inconclusive, and there is high index of suspicion of malignancy.

Treatment

Treatment of tubercular lymphadenitis follows the same category-based principle of ATT, with category 1 regimen for new cases of lymph node TB being 2 months of HRZE, followed by 4 months of HRE. There is no role of surgery in treatment of tubercular lymphadenitis.

◼ ABDOMINAL TUBERCULOSIS

Abdominal TB occurs in approximately 3.5 % of patients with EPTB. Approximately 30% of patients with intra-abdominal TB have evidence of pulmonary TB at the time of diagnosis. Miliary TB cases will have abdominal involvement in about one-third of cases.

Abdominal TB may involve the various regions of the gastrointestinal (GI) tract or the peritoneum, or both. The most common site of involvement in the GI tract is the ileocecal region, followed by ascending colon, jejunum, appendix, duodenum, stomach, esophagus, sigmoid colon, and rectum. In case of peritoneal involvement—it may be wet with development of ascites, dry type with adhesions, and fibrotic type along with pockets of ascites.

Abdominal TB is more common due to the ingestion of infected sputum rather than inhalation of the pathogen. Intra-abdominal TB may also arise from hematogenous spread or in some cases retrograde spread via fallopian tubes.

Abdominal TB may present acutely or insidiously. Clinical features of abdominal TB may be very nonspecific and include abdominal pain, fever, and weight loss. In the case of intestinal involvement, child may present with colicky pain, chronic diarrhea alternating with constipation and abdominal mass. Ascites is frequently present; subacute intestinal obstruction can also be the presenting complaint. Omental involvement may give rise to a characteristic doughy feel to the abdomen. Isolated involvement of the hepatobiliary system by MTB is rare; it usually is part of a more disseminated process. Hepatic involvement may be miliary with multiple miliary tubercles; granulomatous with tuberculomas; nodular with abscess formation; ductal; or nodal where nodes cause obstruction at the porta leading to jaundice.

Diagnosis

Diagnosis of abdominal requires the following:
- *Chest X-ray:* X-ray should be done in all the cases of presumptive abdominal TB to look for pulmonary involvement.
- *Ascitic fluid analysis:* Ascitic fluid is usually straw colored, exudative in nature, with majority of lymphocytes. Protein concentration is higher than 2.5 g/mL, serum-ascites-albumin gradient (SAAG) > 1.1.
- *Microbiological confirmation* should be attempted in all cases. Samples that can be sent for ZN staining, MGIT culture and CBNAAT assay include ascitic fluid, ultrasonography, or CT-guided fine needle aspirate or biopsy from the mesenteric/retroperitoneal nodes or peritoneum.

Treatment

- Category 1 ATT is advised for abdominal TB for a period of 6 months.
- Supportive treatment should be provided for ascites.
- Subacute intestinal obstruction is to be managed conservatively.

◼ OSTEOARTICULAR TUBERCULOSIS

Bones and joints account for approximately 10% of EPTB. Spinal TB or Pott's spine is the most common type of bone TB, thoracic spine being the most common site. Spinal TB results from hematogenous spread from either a pulmonary site or extrapulmonary site, such as lymph node.

Tuberculosis of the spine may present with localized back pain for more than 6 weeks, fever, weight loss, or failure to gain weight. There may be localized tenderness with gibbus formation, with or without spinal cord involvement and neurological manifestations.

All suspected cases of spinal TB should undergo X-ray of spine, followed by MRI of spine. MRI spine demonstrates characteristic features of bone destruction earlier than X-ray

and can also give important information regarding the spinal cord involvement. Chest X-ray should also be done in all cases to look for pulmonary involvement. Samples should be taken (guided by radiology) from any paravertebral collection and joint effusion for AFB, MGIT culture, and CBNAAT assay along with cytopathology.

The treatment option for bone TB is category 1 ATT for a total duration of 12 months (2 months HRZE, followed by 10 months of HRE). Development and progression of neurological deficit may need surgical intervention.

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

Central nervous system TB includes an array of conditions— meningitis (TBM), cerebral and spinal tuberculoma, myelitis, and arachnoiditis. Approximately 1% of total TB cases are due to CNS TB. CNS TB can lead to considerable mortality and morbidity, especially, in younger children < 3 years of age.

Tuberculosis Meningitis

Tuberculosis meningitis may present as acute, subacute, or chronic meningitis. According to the Wallgren timeline, TBM develops within approximately 3 months of primary infection if not contained. TBM may initially present with nonspecific symptoms, such as fever, listlessness or apathy, poor appetite, failure to thrive, neck stiffness, and headache if the child is old enough to complain. Later it may progress to altered sensorium, seizures, and focal neurological deficits. Because of the nonspecific nature of the symptoms any meningitis such as presentation before one year of age should be investigated for TBM. Moreover, there is a close association of TBM with miliary TB and immunocompromised states.

The disease begins with the development of small tuberculous foci (Rich foci) in the brain, spinal cord, or meninges caseating into the subarachnoid space.

There are various clinical classifications of stages or severity of TBM. The British Medical Council Research criteria classify TBM into following stages:
- *Mild:* Fully conscious with no focal neurological deficit.
- *Moderate:* Conscious but with altered sensorium, confusion, lethargy, and moderate neurological signs, such as single nerve palsy, hemiparesis, and paraparesis.
- *Severe:* Comatose, multiple cranial nerve palsies, hemiplegia, and/or paraplegia.

Effort should be made for early diagnosis and treatment of TBM to avoid unfavorable outcome and lasting disability.

Diagnosis
- *Lumbar puncture and cerebrospinal fluid (CSF) analysis:* Clear appearance, pleocytosis with lymphocytic predominance, raised protein (0.5–2.5 g/L, and low CSF—plasma glucose ratio < 0.5). CSF should be sent for AFB, MGIT culture, and CBNAAT assay. Samples should also be sent for ruling out bacterial and fungal pathology.
- *Imaging:* Noncontrast CT brain shows basal hyperdense exudates; contrast studies may demonstrate basal meningeal enhancement, infarcts, or hydrocephalus. MRI brain is a better imaging option in determining the features of TBM, especially brainstem lesions and early infarcts. Contrast-enhanced MRI can help in visualization of leptomeningeal tubercles, vascular involvement (most commonly affecting the terminal portions of the internal carotid arteries and proximal parts of middle and anterior cerebral arteries).
- *Adenosine deaminase* does not have any role in diagnosing TBM.
- Like any other EPTB, a *chest X-ray* should always be done to look for pulmonary involvement.
- *Human immunodeficiency virus infection* should also be ruled out.

Main complications of TBM are hydrocephalus (communicating variety in 70–80% cases), vasculitis, stroke, and opticochiasmatic arachnoiditis leading to loss of vision.

Tuberculoma

Tuberculomas are granulomas in solid organs. CNS tuberculoma can occur anywhere in brain or spinal cord and may be present along with TBM. Clinical features of CNS tuberculoma are mainly seizures and/or focal neurological deficit; fever and headache may also be present.

Diagnosis

Important differential diagnosis includes neurocysticercosis, pyogenic abscess, and malignancy. The differentiating features between CNS tuberculoma and neurocysticercosis are outlined in **Table 5.25.3**. MRI brain is the main modality

Table 5.25.3: Differences between CNS tuberculoma and neurocysticercosis.

CNS tuberculoma	Neurocysticercosis
May present at any age	Rare before 3 years of age
Progressive neurological deficit	Usually no neurological deficit
Lesion size is usually >20 mm, irregular outline with marked cerebral edema, may be conglomerate	Usually smaller, regular rounded outline with less cerebral edema
May be supra- or infratentorial	Usually supratentorial
Likely to cause midline shift	Usually no midline shift
Magnetic resonance spectroscopy shows lipid peak	No lipid peak

(CNS: central nervous system)

of diagnosis of CNS tuberculomas. Tuberculomas may occasionally increase in size or number in the first 3 months after starting ATT; this is due to paradoxical reaction or immune reconstitution inflammatory syndrome.

Treatment of Central Nervous System Tuberculosis

Treatment of any form CNS TB entails 12 months of ATT (2 HRZE + 10 HRE) for new cases. Adjunctive steroid therapy in the form of prednisolone (4 mg/kg) or dexamethasone (0.6 mg/kg) for 4 weeks followed by tapering over next 2 weeks improves the outcome. Mannitol may be used for emergency management of cerebral edema. In more subacute cases and in hydrocephalus, acetazolamide or furosemide may be used. Surgical intervention may be needed for hydrocephalus in the form of ventriculoperitoneal shunting, if there is no response to medical management or if there is noncommunicating hydrocephalus. In the case of seizures, appropriate antiepileptic drug should be added.

TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS

With the spread of the HIV infection, there has been resurgence in TB. The two infections have significantly detrimental interactions. Coexistent TB and HIV infections accelerate the progression of both the diseases. HIV-infected children are more likely to have EPTB and disseminated TB; the course is also likely to be more rapid. An HIV-infected child with latent tubercular infection is more likely to develop the disease than a seronegative child.

Diagnosis

In the absence of significant immunosuppression due to HIV infection, the clinical manifestations of TB are not much different from that in seronegative children. Diagnosis of TB in HIV-infected children poses greater challenges than in other children. Even with the use of a lower cut off of 5 mm, the tuberculin test is often negative, particularly in children with severe immunosuppression. In extensive disease, the bacteriological confirmation rates are likely to be greater. All attempts should be made to isolate MTB. Other than providing definitive diagnosis, it offers the opportunity to do drug-sensitivity analysis. The incidence of MDR TB is higher in HIV-infected patients.

Management

Most current international guidelines recommend that TB in HIV-infected children should be treated according to the same category-based treatment as in non-HIV-infected children. A close follow-up is essential to diagnose nonresponse/drug resistance early. In a HIV-positive child, starting ATT takes precedence over antiretroviral therapy.

There is no clear-cut consensus for the *optimal timing of commencing antiretroviral therapy* when a child is on ATT, but all HIV-infected children who have developed TB have to be started on ART, irrespective of the CD4 count. The decision has to be taken weighing the possibilities of drug interaction, immune reconstitution syndrome, overlapping toxicities against the possibility of worsening immune status. However, it is advisable to start ART as soon as possible within 8 weeks of initiation of ATT. Earlier initiation of ART is more crucial in HIV-TB coinfected children with low CD4 values.

After timing, the next important concern in treatment of HIV-TB coinfected children is the *drug interaction between RIF and antiretroviral drugs,* particularly nevirapine (NVP) and efavirenz (EFV). RIF is known to be a potent inducer of hepatic microsomal cytochrome P450 (CYP 450) enzyme system. NVP and EFV are metabolized primarily by CYP3A4 and CYP2B6, respectively, both being induced by RIF. Some important studies in adults have shown that NVP and EFV levels are reduced by 20–40% when coadministered with RIF; changes in NVP levels are more than that of EFV. In children over 3 years of age or >10 kg body weight, a regimen of two nucleoside reverse transcriptase inhibitors (NRTIs) + EFV (the non-NRTI component) is suggested. Currently, in children under 3 years of age, regimen containing lopinavir with ritonavir boosting is the first choice. In the presence of coadministration of RIF, lopinavir needs to be superboosted with ritonavir (1:1 ratio). If superboosting is not possible, NVP can be used. When used along with RIF, no lead-in period should be given for NVP so that the child is not exposed to subtherapeutic levels. Moreover, NVP should be given at the highest possible dosage ($200\ mg/m^2$/dose). Alternatively, rifabutin can be used instead of RIF as it is less affected by the induction of CYP3A4. All children diagnosed with TB-HIV coinfection should receive cotrimoxazole prophylaxis.

Please refer to Chapter 5.23, Pediatric Human Immunodeficiency Virus Infection or Acquired Immunodeficiency Syndrome, for more specific details.

MULTIDRUG RESISTANCE TUBERCULOSIS

Multidrug resistance TB is defined as a case of TB with MTB showing resistance to at least INH and RIF. In 2016, globally, an estimated 4.1% of new TB cases and 19% of previously treated cases have been diagnosed with MDR TB.

In the absence of a drug-sensitivity report, conventionally the second-line regimen is designed with at least 5–7 antitubercular drugs presumed to be still effective. Apart from ethambutol and pyrazinamide from the first-line drugs, an injectable aminoglycoside, such as kanamycin, a fluoroquinolone, such as levofloxacin, along with ethionamide and cycloserine are added. More drugs may be

added in case-to-case basis. The usual duration of second-line ATT is 18–24 months. A child on this therapy should be very carefully monitored for clinical improvement and adverse events of the drugs prescribed.

PREVENTION

Prophylaxis

Isoniazid is prescribed for chemoprophylaxis at a dose of 10 mg/kg of body weight/day, for 6 months.

Tuberculosis preventive therapy or chemoprophylaxis should be provided in the following scenarios:
- All asymptomatic contacts, less than 6 years of age, of an open case of TB (smear positive), after ruling out active disease. Status of BCG vaccination or TST reading does not preclude one from receiving this chemoprophylaxis.
- All HIV-infected children with a known exposure to an infectious TB case, but with no active TB disease.
- All TST-positive children who are receiving immunosuppressive therapy.

- A child born to mother who was diagnosed to have TB in pregnancy, after ruling out congenital TB. BCG vaccination can be given at birth even if chemoprophylaxis is planned.

Vaccination

Bacille Calmette–Guérin is the only vaccine for TB disease used at present. The protection it provides against pulmonary TB is variable; however, it has 60–80% protective efficacy against more serious, disseminated diseases in children such as CNS TB.

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5.26

Diphtheria

Monjori Mitra

INTRODUCTION

Diphtheria is a potentially acute disease caused by exotoxin-producing *Corynebacterium diphtheriae*, a gram-positive *Bacillus*. Morbidity and mortality result from the bacterial toxin that may cause obstructive pseudomembranes in the upper respiratory tract (croup) or damage myocardium and other tissues.

EPIDEMIOLOGY

Humans are the only natural reservoir of *C. diphtheriae*, although occasionally it has been isolated from a variety of domestic animals. Spread occurs in close-contact settings through respiratory droplets or direct contact with respiratory secretions or skin lesions. The majority of nasopharyngeal

C. diphtheriae infections result in asymptomatic carriage, with clinical disease developing in only about one in seven individuals.

Diphtheria immunization protects against disease but does not prevent carriage. Vaccination with diphtheria toxoid (formalin-treated toxin) was introduced in the 1920s. Immunization of children in an era when the majority of older individuals had natural immunity resulted in a dramatic drop in the incidence of diphtheria and an even more rapid decline in the proportion of toxigenic strains isolated, presumably because the selective advantage of the *tox* gene promotion of greater replication and spread of the organism is lost in an immune host. In most Western countries, toxigenic *C. diphtheriae* has virtually been eliminated.

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