

# CHAPTER 18

## TUBERCULOSIS

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### Introduction

Tuberculosis (TB) is a dreadful disease that is still rampant in the developing world.<sup>1-4</sup> It can involve almost any organ or tissue in the body from the brain to the bones. The problem is more significant in children in developing countries, as they are the neglected lot who are often entrapped with infection, be it pneumonia or gastroenteritis. This delays the diagnosis of the disease and increases the tendency of the disease to spread into miliary infection in the sick undernourished child.

Tuberculosis was declared a global public health emergency in 1993 by the World Health Organization (WHO).<sup>5</sup> According to the WHO, developing countries, including India, China, Pakistan, Philippines, Thailand, Indonesia, Bangladesh, and the Democratic Republic of Congo, account for nearly 75% of all cases of TB. There are about 0.5 million deaths worldwide every year from this disease.<sup>6</sup>

Tuberculosis is still a major cause of morbidity in developing countries. Today, 19–43.5% of the world's population is infected with *Mycobacterium tuberculosis*, with more than 8 million new cases of TB occurring each year.<sup>7</sup> The incidence and severity of pulmonary infections such as TB are expected to increase with the increasing incidence of human immunodeficiency virus (HIV) infection.<sup>8</sup> The highest TB incidences and HIV infection prevalence are recorded in sub-Saharan Africa (with about 35% of mothers known to be infected with HIV), and as a consequence, children in this region bear the greatest burden of TB/HIV infection.<sup>9</sup> The incidence is rising in Western countries due to immigration from Third World countries and the rising trend of HIV infection. There has been a decrease in mortality in cases of pulmonary tuberculosis without HIV due to recent improved health care and prompt initiation of therapy.

Diagnosis of tuberculosis in children is difficult because children are less likely to have obvious symptoms of TB. Tubercular infection has been identified in all organs in children. Genitourinary tuberculosis, although rare in children, has vague symptoms and presentation with the delayed diagnosis due to the late presentation leading to cicatrization sequelae.<sup>10</sup> Children and young adults comprised 70% of the study population in a large series of craniovertebral junction tuberculosis.<sup>11</sup> This chapter focusses only on chest and abdominal tuberculosis.

The children most at high risk for tuberculosis include:

- children living in a household with an adult who has active tuberculosis;
- children of poor socioeconomic status;
- children residing in rural areas;
- undernourished children;
- children living in small enclosed areas and in areas with poor ventilation;
- children living in a high endemic region;
- children infected with HIV or in an immunocompromised state following chemotherapy or prolonged steroid use;
- children with infections such as measles, varicella, and pertussis, which may activate quiescent TB; and

- children with certain human leukocyte antigen (HLA) types that have a predisposition to TB.

### Tubercular Bacilli

*Mycobacterium tuberculosis* is the most common cause of TB. Other rare causes are *M. bovis* and *M. avium*. *M. bovis* infection has been traced to the use of cheese made from unpasteurised milk. *M. tuberculosis* is an aerobic, non-spore-forming, nonmotile, slow-growing bacillus with a curved and beaded rod-shaped morphology. It can survive under adverse environmental conditions. The acid-fast characteristic of the mycobacteria is its unique feature. Humans are the only known reservoirs for *M. tuberculosis*.

### Epidemiology

The overall incidence of tuberculosis is as high as 0.7–2 per 1,000 children in the developing countries, with chest, meninges, and lymph nodes being commonly involved.<sup>12</sup> The disease is predominant in females. Infants are more susceptible to tuberculous bacilli and may develop severe extrapulmonary and miliary forms of the disease.<sup>13</sup> Tubercular infection of the abdominal cavity accounts for 15% of all intestinal obstructions.<sup>12</sup> It is more common in children, affecting those >5 years of age and particularly those residing in rural areas.<sup>3</sup>

Tuberculosis in infants and children <4 years of age is much more likely to spread throughout the body through the bloodstream. Thus, children are at much greater risk of developing miliary tuberculosis. Hence, prompt diagnosis and treatment of tuberculosis is essential.

### Routes of Infection

The route of infection for pulmonary tuberculosis is inhalation of airborne bacteria. After inhalation, the bacilli are usually deposited in the mid-lung zone, into the subpleural distal respiratory bronchiole or alveoli. The alveolar macrophages then phagocytose the inhaled bacilli but are unable to kill them, thus the bacilli continue to multiply unimpeded. The infected macrophages are then transported to the regional lymph nodes. The initial pulmonary site of infection and its adjacent lymph nodes are known as the primary complex or Ghon focus.

Progression of the primary complex may lead to enlargement of hilar and mediastinal nodes with resultant bronchial collapse. Progressive primary TB may develop when the primary focus cavitates and the organisms spread through the contiguous bronchi.

Lympho-hematogenous dissemination of the mycobacteria may occur to other lymph nodes, and regions in the body (e.g., kidney, epiphyses of long bones, vertebral bodies, meninges, and, occasionally, the apical posterior areas of the lungs) or may spread widely as miliary TB. This may occur when caseous material reaches the bloodstream from a primary focus or a caseating metastatic focus in the wall of a pulmonary vein (Weigert focus). Bacilli may remain dormant in the apical posterior areas of the lung for several months, or even years, with later progression of disease.

The gastrointestinal tract is involved in more than 60% of cases of abdominal tuberculosis. The postulated routes of infection into the gastrointestinal tract include:

- hematogenous spread from reactivation of old primary lung focus;
- ingestion of infected sputum from active pulmonary focus;
- contiguous spread from adjacent organs; and
- through lymph channels from infected nodes.

The most common site is the terminal ileum and ileocaecal region due to increased physiological stasis, increased fluid and electrolyte absorption, minimal digestive activity, and an abundance of lymphoid tissue at this site. The other sites, in order of frequency, include the colon and jejunum. Rarely, tuberculosis may involve other areas such as the perianal region, appendix, duodenum, stomach, and oesophagus. The nodal involvement due to tuberculosis is commonly mesenteric or retroperitoneal. The abdominal solid organs (liver, spleen, and pancreas) may also be affected with tuberculosis, but rarely.

### Pathophysiology

Nearly all cases of abdominal TB are due to the human strain of *M. tuberculosis*, although atypical mycobacteria account for a few cases. Infection due to the *bovis* species is rare, largely due to the practice of boiling milk. In India, the organism isolated from all intestinal lesions has been *M. tuberculosis* and not *M. bovis*.<sup>14</sup> The peritoneum is commonly involved, although any part of the abdominal cavity, such as hollow viscera, lymph nodes, and solid viscera, may be involved. An accurate diagnosis requires a high index of suspicion, as most of the investigations are nonspecific and less sensitive.

Tuberculous granulomas of variable size are initially formed in the submucosa or the Peyer's patches. Tubercular ulcers are relatively superficial, transversely oriented, and do not penetrate beyond the muscularis. Cicatricial healing of these circumferential ulcers results in strictures. Mesenteric lymph nodes may be enlarged or matted, and may caseate.

A cell-mediated immune response terminates the unimpeded growth of *M. tuberculosis* within 2 to 3 weeks after the initial infection. Cluster of differentiation 4 (CD4) helper T cells activate the macrophages to kill the intracellular bacteria with resultant epithelioid granuloma formation. CD8 suppressor T cells lyse the macrophages infected with the mycobacteria, resulting in the formation of caseating granulomas. Mycobacteria cannot continue to grow in the acidic extracellular environment, and thus most infections are controlled. The only evidence of infection is a positive tuberculin skin (Montoux) test result.

### Clinical Presentation

Tuberculosis patients are usually malnourished, as they belong to lower socioeconomic strata. Primary pulmonary tuberculosis may present with generalised symptoms, such as fever of unknown origin, failure to thrive, night sweats, anorexia, significant weight loss, nonproductive cough, or unexplained lymphadenopathy. Pulmonary TB may manifest as endobronchial TB with focal lymphadenopathy, progressive pulmonary disease, pleural involvement, and reactivated pulmonary disease. Progression of the pulmonary parenchymal infection leads to enlargement of the caseous area and may lead to pneumonia, atelectasis, and air trapping in young children. Children usually appear ill with symptoms of fever, cough, malaise, and weight loss. Tubercular pleural effusion may present with acute onset of fever, chest pain that increases in intensity on deep inspiration, and shortness of breath. Fever usually persists for 14–21 days. Reactivation TB usually has a subacute presentation with weight loss, fever, cough, and, rarely, haemoptysis. Reactivation TB typically occurs in older children and adolescents.

Isolated mediastinal tuberculous lymphadenitis is a relatively common entity in children, second in frequency after cervical localisation. In the absence of an accompanying parenchymal lesion, mediastinal tuberculous lymphadenitis may pose a diagnostic dilemma on admission and must be distinguished from other causes of mediastinal masses. Bronchoscopy is suggested as a diagnostic

tool when tuberculosis cannot be excluded by radiology or specific tuberculin skin tests (TSTs). Thoracotomy and excision are reported as necessary to treat the obstructive symptoms. Thoracoscopic mediastinal node biopsy has also been reported as feasible in an infant.<sup>15</sup> Infants <6 months of age may present with respiratory failure, requiring ventilatory support.<sup>16</sup>

Extrapulmonary TB includes peripheral lymphadenopathy, tubercular meningitis, miliary TB, skeletal TB, and other organ involvement. Any child with pneumonia, pleural effusion, or a cavitary or mass lesion in the lung that does not improve with standard antibacterial therapy should be evaluated for tuberculosis.

The clinical presentation of abdominal tuberculosis can be acute, chronic, or acute on chronic. Most patients have constitutional symptoms of low- or high-grade fever (40–70%), weight loss (40–90%), night sweats, anorexia, and malaise. The delay in presentation can vary between 1 and 14 months. Abdominal symptoms include diarrhoea, constipation, alternating constipation and diarrhoea, and pain, which can be either colicky due to luminal compromise or dull and continuous when the mesenteric lymph nodes are involved. A physical examination may show features of ascites, lump abdomen, or visible peristalsis with dilated bowel loops. Miliary tuberculosis presenting with multiple intestinal perforations as an initial manifestation of the disease has also been reported in an infant.<sup>13</sup>

### Tuberculosis of the Abdomen

Any part of the abdomen may get involved in tubercular pathology. The chronic intestinal lesions produced by tuberculosis are of three types: ulcerative, hypertrophic, and stricturous. The ulcerative form is seen more often in malnourished patients, whereas the hypertrophic form is seen in relatively well-nourished patients. Colonic and ileocaecal lesions are ulcerohypertrophic. In tuberculous peritonitis, the gross pathology is characterised by omental thickening and peritoneal tubercles.<sup>14,17,18</sup>

#### Peritoneal Tuberculosis

Peritoneal tuberculosis occurs in four forms:

1. *Wet type peritonitis with generalised ascitis*: The distended abdomen is in sharp contrast to that of a malnourished child, with little muscle mass and subcutaneous fat.
2. *Encysted (loculated) ascitis type*: The child may present with an asymptomatic localised abdominal lump, which may be due to loculated ascites, enlarged lymph node, or matted omentum and intestines.
3. *Dry type with adhesions*: The child presents with subacute abdominal obstruction or a history of feeling a moving ball of wind abdominally.
4. *Classic "plastic" form*: This is a fibrotic type with abdominal masses composed of mesenteric and omental thickening, with matted bowel loops felt as lump(s) in the abdomen. The adolescent has gastrointestinal (GI) symptoms along with a doughy feel of the abdomen. The latter is due to diffuse peritonitis with thickening and adhesions of omentum, mesentery, and peritoneum. The classic presentation is, however, with attacks of subacute intestinal obstruction, most of which resolve on conservative management. A lump is found in 25–33% of cases, most often in the right iliac fossa, in ileocaecal and small bowel TB.

A combination of these types is also common. Tubercular peritonitis and nodal forms are more commonly seen in children and adolescents as compared to the gastrointestinal form.

#### Mesenteric and other lymphadenitis

Nodal forms can present as a lump or intestinal obstruction due to kinks and adhesions. Bowel loops may get involved in the inflammatory process and form a local lump in the right iliac fossa, producing subacute obstruction. Obstructions of the bile duct, pancreatic duct, duodenum, inferior vena cava, or ureter by lymph nodes may also occur, but are rare.

### Acute abdomen

Uncommonly, the presentation may be like an acute abdomen, which may be due to rupture of a caseous lymph node, GI perforation, tubercular peritonitis, ruptured mesenteric abscess, or acute obstruction, especially in the presence of stricture. Involvement of the appendix is usually a part of ileocaecal involvement, and rarely may present as an isolated case of acute appendicitis.

### Gastrointestinal involvement

The patient may present with nonspecific symptoms of vague abdominal pain, mild discomfort, anorexia, malaise, and fever. After a relay of investigations, if no cause is identified, an exploratory laparotomy is done in view of the persisting symptoms (Figure 18.1). The positive findings may be only congestion and neovascularisation. Symptoms will subside on starting antitubercular treatment.



Figure 18.1: A 2-year-old child presenting with subacute intestinal obstruction due to ileocaecal tuberculosis confirmed on laparotomy.

### Oesophageo-Gastroduodenal Tuberculosis

Involvement of oesophagus is extremely rare and presents as dysphagia, odynophagia, and a midoesophageal ulcer. Gastroduodenal tuberculosis may present with dyspepsia and gastric outlet obstruction. Surgical bypass has been required in the majority of cases to relieve obstruction, but successful endoscopic balloon dilatation of duodenal strictures has also been done.

### Jejunioileal Tuberculosis

Tubercular involvement of the jejunum and ileum may present with malabsorption and subacute intestinal obstruction. On exploration, there may be jejunoileitis with nonspecific inflammatory changes on biopsy.

### Terminal Ileal and Ileocaecal Tuberculosis

In India, around 3–20% of all cases of bowel obstruction are due to tuberculosis.<sup>19</sup> Tubercular intestinal stricture presents with recurrent subacute intestinal obstruction in the form of obstipation, vomiting, abdominal distention, and colicky abdominal pain associated with gurgling, feeling like a ball of wind is moving in the abdomen, and visible intestinal loops. Having a chronic inflammatory pathology, tubercular perforations are rare and usually single and proximal to a stricture.

### Segmental Colonic Tuberculosis

This type of tuberculosis commonly involves the sigmoid, ascending and transverse colon. Manifestations include chronic constipation, fever, anorexia, weight loss, and change in bowel habits. It may

simulate late presentation of Hirschsprung's disease in young children, Crohn's disease, amoeboma, or malignancy in adolescents.

### Rectal and Anal Tuberculosis

Rectal tuberculosis is rare and may present with haematochezia, constitutional symptoms and constipation with anal discharge, multiple fistula with ragged margins, or perianal swelling. Digital examination may reveal an annular stricture, which is usually tight and of variable length with focal areas of deep ulceration.

### Miscellaneous Presentations

An uncommon presentation of abdominal tuberculosis is as pyrexia of unknown origin. Suggestive hepatomegaly may lead to the diagnosis of hepatic tuberculosis on liver biopsy. The miliary and local forms of hepatic tuberculosis have quite similar clinical presentations and pathological features. Hepatosplenic tuberculosis is common as a part of disseminated and miliary tuberculosis.

Female patients with abdominal tuberculosis may present with menstrual disorders or later with infertility as a result of involvement of the uterus or fallopian tubes.

## Investigations

Diagnosis is usually made through a combination of radiologic, endoscopic, microbiologic, histologic, and molecular techniques.

### Haematological Tests

Anaemia and hypoalbuminaemia may be associated with tuberculosis due to poor nutrition. Total leucocyte count is raised in half the cases. There may also be associated leucocytosis due to superadded infection along with lymphocytosis suggestive of chronic infection.

A raised erythrocyte sedimentation rate (ESR), although nonspecific, is a very supportive finding and is a good marker to assess the response to treatment. Serologic tests have a limited role due to their inability to distinguish between past and present infections.

### Mantoux Test

An induration of less than 6 mm in diameter indicates either (1) an uninfected patient, (2) recent infection, (3) anergy due to malnutrition or disease states such as measles, or (4) overwhelming tuberculosis infection (50% of autopsies proved cases of severe tuberculosis had been Mantoux negative). Induration in the range of 6–9 mm indicates either past infection or a Calmette-Guérin bacillus (BCG) tuberculosis vaccination. It may also be found in some cases of active infection, particularly where atypical mycobacteria are involved. Induration of 10–14 mm in children <5 years of age strongly indicates active infection. Patients with an induration >14 mm are four times more likely to have an active disease than those with a Mantoux test in the range of 10–14 mm. If the patient has been vaccinated with BCG before, then an induration of more than 15 mm at 1 year, or 12 mm at 2 years after vaccination is considered positive.

Specimens for bacteriologic examination include sputum, gastric lavage, bronchoalveolar lavage, lung tissue, and lymph node. Gastric aspirates may be used in place of sputum in children <6 years of age with pulmonary tuberculosis, as they may not be able to cough out sputum. An early-morning sample should be obtained for undiluted bronchial secretions accumulated during the night. As gastric acidity is poorly tolerated by the tubercle bacilli, neutralisation of the specimen should be done immediately with 10% sodium carbonate or 40% anhydrous sodium phosphate. Even with utmost care, the tubercle bacilli can be detected in only 70% of infants and in only 30–40% of children with disease. Sputum specimens and bronchoalveolar lavage may be used in older children. Nasopharyngeal secretions and saliva are not acceptable.

### Acid-Fast Bacilli Staining

Acid-fast bacilli (AFB) Ziehl-Neelsen staining provides preliminary confirmation of the diagnosis, although it cannot differentiate *M. tuberculosis*

from other acid-fast organisms, such as other mycobacterial organisms or *Nocardia* species. It can give a quantitative assessment of the number of bacilli being excreted (e.g., 1+, 2+, 3+). For a reliable positive result, smears require approximately 10,000 organisms per milliliter. Therefore, the results may be negative in early stages of the disease or with sparse bacilli. A single organism on a slide is highly suggestive and warrants further investigation.

### Mycobacterium Culture

Culture of *M. tuberculosis* is the definitive method to detect bacilli and is more sensitive than examination of the smear. Approximately 10 AFB per millimeter of a digested concentrated specimen are sufficient to detect the organisms by culture. A culture also allows identification of specific species and testing for drug sensitivity. Due to the emergence of multidrug-resistant (MDR) organisms, determination of the drug sensitivity panel of an isolate is important so that appropriate treatment can be ensured.

*M. tuberculosis* is a slow-growing organism, however, so a period of 6–8 weeks is required for colonies to appear on conventional culture media. Conventional solid media include the Löwenstein-Jensen medium, which is egg based, and the Middlebrook 7H10 and 7H11 media, which are agar based. Liquid media (e.g., Dubos oleic-albumin media) also are available, and they require incubation in 5–10% carbon dioxide for 3–8 weeks.

### Nucleic Acid Techniques

Nucleic acid techniques include nucleic acid probes and polymerase chain reaction (PCR). Although their sensitivity and specificity in smear-positive cases exceed 95%, the sensitivity of smear-negative cases varies from 40% to 70%.

- *Nucleic acid probes* help advance identification of the *M. tuberculosis* complex. Sensitivity and specificity approach 100% when at least 100,000 organisms are present.
- *PCR nucleic acid amplification tests* allow the direct identification of *M. tuberculosis* in clinical specimens, unlike nucleic acid probes, which require substantial time for bacterial accumulation in broth culture.

### Enzyme-Linked Immunoassay Test

A new test, Quantiferon (QFT-g), was approved in 2005 by the US Food and Drug Administration (FDA). The test basically detects the presence of interferon gamma release protein (IFN-g) from the blood of sensitised patients when incubated with the early secretory antigenic target-6 (ESAT6) and culture filtrate protein 10 (CFP10) peptides. The test is as sensitive as, and more specific than, the tuberculin skin test and has been recommended as a screening tool for diagnosing disease as well as infection. No available serodiagnostic test for TB has adequate sensitivity and specificity for routine use in diagnosing TB in children.

### Chest Radiograph

Evidence of tuberculosis in a chest radiograph supports the diagnosis, but a normal chest radiograph does not rule it out. It may show signs of active tuberculosis in 15% of patients.<sup>20</sup> The findings can be (1) miliary tuberculosis in a sick child without eosinophilia; (2) atelectasis, emphysema, bronchiectasis, or parenchymal opacity—any of these when present with pleural effusion or hilar lymphadenopathy indicates active disease; or (3) patchy consolidation or infiltration, which can be nonspecific but when associated with a positive Mantoux test and cavitation in the apex indicates activity. Signs of “old” tuberculosis (e.g., obliterated costophrenic angle, calcified hilar lymph nodes, or a fibro-calcific lesion) are present in 20% of patients.<sup>20</sup>

### Plain Radiograph Abdomen

An erect radiograph is also invaluable at the time of abdominal pain in demonstrating dilated jejunal and ileal loops with multiple air fluid levels, with an absence of gas in the colon and fixed bowel loop in cases of obstruction, pneumoperitoneum in cases of perforation, and

any intussusception. Enteroliths, mottled calcification in the mesenteric lymph nodes, and any evidence of ascitis may be suggested on the plain film.

### Contrast Studies

Barium meal and enema are together positive in 80–85% of the cases of GI tuberculosis.

- *Small bowel barium meal*: The radiologic findings that may be seen on a small bowel study include:
  - mucosal irregularity and rapid emptying (ulcerative);
  - flocculation and fragmentation of barium (malabsorption);
  - stiffened and thickened folds;
  - luminal stenosis with smooth but stiff contours (“hour glass-stenosis”);
  - dilated loops and strictures;
  - displaced loops (enlarged lymph nodes); and
  - adherent fixed and matted loops (adhesive peritoneal disease).
- *Barium enema*: The following characteristics may be seen:
  - spasm and oedema of the ileocaecal valve (early involvement); characteristic thickening of the ileocaecal valve lips or wide gaping of the valve with narrowed terminal ileum (“Fleischner” or “inverted umbrella sign”);
  - “conical caecum”, a deformed and pulled-up caecum due to contraction and fibrosis;
  - increased (obtuse) ileocaecal angle and dilated terminal ileum, appearing suspended from a retracted, fibrosed caecum (“goose neck deformity”);
  - deformed and incompetent ileocaecal valve;
  - “purse string stenosis”—localised stenosis opposite the ileocaecal valve with a rounded-off smooth caecum and a dilated terminal ileum;
  - “Stierlin’s sign”—appears as a narrowing of the terminal ileum with rapid emptying into a shortened, rigid, or obliterated caecum; and
  - “string sign”—a narrow stream of barium, indicating stenosis

Both Stierlin and String signs can also be seen in Crohn’s disease. Enteroclysis followed by a barium enema may be the best protocol for evaluation of intestinal tuberculosis.

### Ultrasonography

Ultrasound is more helpful in peritoneal and nodal tuberculosis, but it may also identify thickened and dilated bowel loops. The following features may be seen:

- Free or loculated ascitis.
- “Club sandwich” or “sliced bread” sign, due to localised fluid between radially oriented bowel loops.
- Lymphadenopathy may be discrete or conglomerated (matted). The echotexture is mixed heterogenous, in contrast to the homogeneously hypochoic nodes of lymphoma. Both caseation and calcification are highly suggestive of a tubercular aetiology.
- Bowel wall thickening—best appreciated in the ileocaecal region.
- Thickening of the small bowel mesentery of 15 mm or more.
- Pseudo-kidney sign—involvement of the ileocaecal region that is pulled up to a subhepatic position.

Ultrasound-guided fine-needle aspiration (FNA) biopsy has been used successfully in the diagnosis of abdominal tuberculosis. Ultrasonography may also be useful for guiding procedures such as ascitic tap and FNA cytology or biopsy from the lymph nodes or hypertrophic lesions.

### Computed Tomographic Scan

Ileocaecal tuberculosis is usually hyperplastic and well evaluated on a computed tomography (CT) scan. Circumferential thickening of caecum and terminal ileum, adherent loops, large regional nodes, and mesenteric thickening can together form a mass centred around the ileocaecal junction. A CT scan can also pick up ulceration or nodularity within the terminal ileum, along with narrowing and proximal dilatation. Involvement around the hepatic flexure of the colon is common. Complications of perforation, abscess, and obstruction can also be seen. Tubercular ascitic fluid is of high attenuation value (25–45 HU) due to its high protein content. Thickened peritoneum and enhancing peritoneal nodules may be seen. A smooth peritoneum with minimal thickening and marked enhancement after contrast suggests tuberculous peritonitis, whereas nodular and irregular peritoneal thickening suggests the presence of peritoneal carcinomatosis.<sup>21</sup> Omental thickening is well seen often as an omental cake appearance.<sup>22</sup>

Lymph nodes may be interspersed. The four patterns of contrast enhancement of tuberculous lymph nodes on the contrast-enhanced CT (CECT) have been described as (in order of frequency): (1) peripheral rim enhancement, (2) nonhomogenous enhancement, (3) homogenous enhancement, and (4) homogenous nonenhancement.<sup>23</sup> Different patterns of contrast enhancement may be seen within the same nodal group, possibly related to the different stages of the pathological process. Caseating lymph nodes are seen as having hypodense centres and peripheral rim enhancement. The presence of nodal calcification in the absence of a known primary tumour in patients from endemic areas suggests a tubercular aetiology. CT findings can help differentiate it from other inflammatory and neoplastic diseases, particularly lymphoma and Crohn's disease.<sup>24</sup> In tuberculosis, the mesenteric, mesenteric root, celiac, porta hepatic, and peripancreatic nodes are characteristically involved, reflecting the lymphatic drainage of the small bowel. The tuberculous involvement of the pancreas may show as well-defined hypoechoic areas on ultrasonography and as hypodense necrotic regions within the enlarged pancreas. CT is more accurate than ultrasound in detecting abnormalities such as periportal and peripancreatic lymph nodes and bowel wall thickening. However, bowel wall dilatation can be better appreciated on ultrasound than on a CT scan. Magnetic resonance imaging (MRI), when compared to a CT scan, provides no additional information.<sup>25</sup>

### Cytology and Biochemistry of Ascitic Fluid

The ascitic fluid in abdominal tuberculosis is clear or straw-coloured. Its glucose concentration is less than 30 mg/dl, and its high protein content is >3 g/dl, with a total cell count of 150–4000/cu mm, usually more than 1,000/cu mm (consisting predominantly of lymphocytes (>70%)). The ascites-to-blood glucose ratio is less than 0.96.<sup>26</sup> The serum ascitis albumin gradient is less than 1.1 g/dl, and adenosine deaminase levels are above 36 U/l. Adenosine deaminase (ADA) is increased in tuberculous ascitic fluid due to the stimulation of T-cells by mycobacterial antigens. In coinfection with HIV, the ADA values can be normal or low. High interferon levels in tubercular ascitis have been found to be useful diagnostically. Combining both ADA and interferon estimations may further increase the sensitivity and the specificity. The AFB smear and culture are positive in only 10–15% cases, but the yield rises dramatically by culturing a litre of fluid concentrated by centrifugation.<sup>27</sup> Fluorescent staining with auramine-O is superior to Ziehl-Neelsen staining with regard to the positivity and the ease of detection. In children, AFB may be recovered from stomach wash, keeping in mind that scant saprophytic mycobacteria may also be present as normal flora.

PCR conducted with ascites fluid has produced DNA sequences compatible with tuberculosis.<sup>28</sup> PCR can be a rapid and reliable method for identification of peritoneal tuberculosis; acceleration of the diagnostic decision-making process prevents exposure to unnecessary surgery and allows early initiation of antituberculosis treatment.

### Imaging Bacterial Infection with Infecton

A new radioimaging agent, Tc-99m ciprofloxacin (Infecton) has been used to detect deep-seated bacterial infections, such as intraabdominal abscesses. Patients with suspected bacterial infection have been subjected to Infecton imaging and microbiological evaluation, reporting an overall sensitivity of 85.4% and a specificity of 81.7% for detecting infective foci.<sup>29</sup> Sensitivity was higher (87.6%) in microbiologically confirmed infections. Infecton may aid in the earlier detection and treatment of deep-seated infections, and serial imaging with Infecton might be useful in monitoring clinical response and optimising the duration of antimicrobial treatment.

### Colonoscopy

Although the appearance is nonspecific, colonoscopy has been used for the diagnosis of colonic or ileocaecal tuberculosis. Most commonly, ulcers, strictures, or oedematous and polypoid mucosal folds are seen. Mucosal pinkish nonfriable nodules of variable sizes with ulcerations in between the nodules in a discrete segment of colon, most often in the caecum, are pathognomic. Areas of strictures, pseudopolypoid oedematous folds, and a deformed and oedematous ileocaecal valve may be seen.

Multiple biopsies should be taken from the edge of the ulcers. The tissue should also be examined for AFB smear and culture, as the histology may not be characteristic.

Endoscopic biopsy specimens may be subjected to PCR for detection of AFB.<sup>30</sup> The limitations of colonoscopic biopsy are that previous antitubercular therapy can alter the histology, and that granulomas are often found in the submucosa. Of 82 patients with GI tuberculosis, colonoscopy was diagnostic in only 47.<sup>31</sup>

### Laparoscopy

Laparoscopy is a very useful investigation in doubtful cases. Visual appearances have been found to be more helpful than histology, culture, or guinea pig inoculation.<sup>32</sup>

The laparoscopic findings in peritoneal tuberculosis can be grouped into three categories: (1) thickened peritoneum with tubercles, (2) thickened peritoneum without tubercles, and (3) fibroadhesive peritonitis with markedly thickened peritoneum and multiple thick adhesions fixing the viscera.

### Markers for Treatment Response

ESR tends to fall with response to antitubercular treatment. A significant decrease in the concentrations of C-reactive protein (CRP), ceruloplasmin, haptoglobin, and alpha-1-acid glycoprotein has been seen with antitubercular treatment.

### Differential Diagnosis

Hypertrophic intestinal tuberculosis may mimic malignant neoplasms such as lymphoma or carcinoma. The ulcero-hypertrophic form may mimic inflammatory bowel disease. The nodal form may closely mimic lymphomas. The ascitic form can be difficult to distinguish from malignant peritoneal disease and sometimes ascites due to chronic liver disease. In cases of hepatosplenomegaly, all other causes need to be excluded before considering a tubercular aetiology. Sometimes, when all investigations are negative and TB is strongly suspected, a laparotomy may be indicated.

## Treatment

### Laparotomy

In circumstances where the clinical suspicion of intraabdominal disease is strong, but results of investigations are equivocal, a diagnostic laparotomy may be a safer option for abdominal tuberculosis. Where clinical suspicion is strong and imaging features are suggestive, a therapeutic trial of antitubercular treatment (ATT) may be justified. However, laparotomy is definitely indicated where the diagnosis is in doubt and if the malignancy cannot be ruled out with certainty. In many patients, it may not be possible to rule out malignancy, even at laparotomy. A

frozen section examination may help in such cases. A mesenteric lymph node should preferably be removed in such cases, as caseation and granulomas are much more likely to be present in lymph nodes than in the intestinal lesions. An omental nodule may also be taken for biopsy. The correction of a stenotic bowel lesion may be done if found.

It is important to remember that:

- Laparotomy is better performed under empirical cover of antitubercular drugs for about 2 weeks, wherever feasible.
- The aim of surgery in tubercular abdominal patients is to do minimal intervention and avoid any major operative procedure. Perhaps only a bypass surgery is enough just to relieve the symptoms. Tubercular pathology cannot be eradicated by surgery alone.
- External diversion (ileostomy or double-barrel stoma), internal diversion with side-to-side bowel anastomosis, closure of the perforation, and stricturoplasty are the commonly performed procedures. Surgical resection is less commonly performed.
- Laparoscopy is not indicated due to the high possibility of adhesions inside the peritoneal cavity. The risk of perforation of the bowel is also high while being handled with instrumentation. Tract contamination may result in chronic tubercular fistula.

### Medical Treatment

Antimicrobial treatment is the same for pulmonary and abdominal tuberculosis. Medical treatment with a standard full course of ATT is indicated in all patients. In peritoneal tuberculosis, only medical treatment is required. Intestinal tuberculosis is a systemic disease. In GI tuberculosis, surgery may be required and preferably is done 6–8 weeks after starting the antitubercular therapy. Although the use of short course regimens for 6–9 months have been found to be equally effective by few studies, many physicians still extend the treatment duration to 12 to 18 months, according to the conventional regimens in cases of abdominal tuberculosis.<sup>33</sup> This is justified in view of the unpredictable absorption due to the diseased gut and associated symptoms such as vomiting and malabsorption.

The main antitubercular drugs are isoniazid (INH), rifampicin, ethambutol, pyrazinamide (PZA), and streptomycin (SM). Thiacetazone and p-aminosalicylic acid (PAS) are not recommended for use for abdominal tuberculosis. In a study of 350 patients with extrapulmonary tuberculosis (including 47 children),<sup>34</sup> a 9-month regimen using only INH and rifampicin was successful in 95% of the cases, with only 0.7% of the cases relapsing during a follow-up of 9 years.

Patients with peritoneal, nodal, or ulcerative intestinal disease are usually treated with drugs (e.g., ATT). Corticosteroids have also been used to reduce subsequent complications of adhesions in patients with peritoneal disease. No controlled studies have been performed to show the additional benefit of using steroids. Patients with intestinal obstruction due to strictures and hypertrophic lesions require surgical treatment. Successful treatment of obstructing intestinal lesions with ATT alone has also been seen. Patients usually report improvement in systemic symptoms in a few weeks, but relief of intestinal symptoms may require a much longer duration.

Monitoring with liver function tests (LFTs) is necessary, especially if the patient has suspected icterus or malaise, anorexia, or abdominal pain. INH, rifampicin, and pyrazinamide should be discontinued temporarily in the presence of icterus or a threefold rise in transaminases. As the antitubercular therapy causes healing with fibrosis, this may result in further narrowing and intestinal stricture. Therapy can also alter the histopathological picture and may even increase the perforation rate.

### Directly Observed Therapy

Since noncompliance to these regimens is a common cause of treatment failure, directly observed therapy (DOT) is recommended. This involves administration of medication under supervision by a health

care provider or a nurse. DOT should be used with all children suffering from tuberculosis. The lack of availability of the paediatric dosage forms of most antituberculosis medications necessitates using crushed pills and suspensions. Even when drugs are given under DOT, tolerance of the medications must be monitored closely. Intermittent regimens should be monitored by DOT for the duration of therapy because poor compliance may result in inadequate drug delivery.

### Surgery for Pulmonary Tuberculosis

It must be emphasized that medical therapy remains the mainstay of treatment in pulmonary tuberculosis, and surgical treatment is primarily used to handle complications and hasten recovery.

In children, the primary complex is usually directly or indirectly the main etiologic factor responsible for the need for surgical intervention. Indications for surgical intervention are limited in children, and the challenge lies in determining the timing and nature of intervention.

Indications for surgery in paediatric pulmonary tuberculosis include:

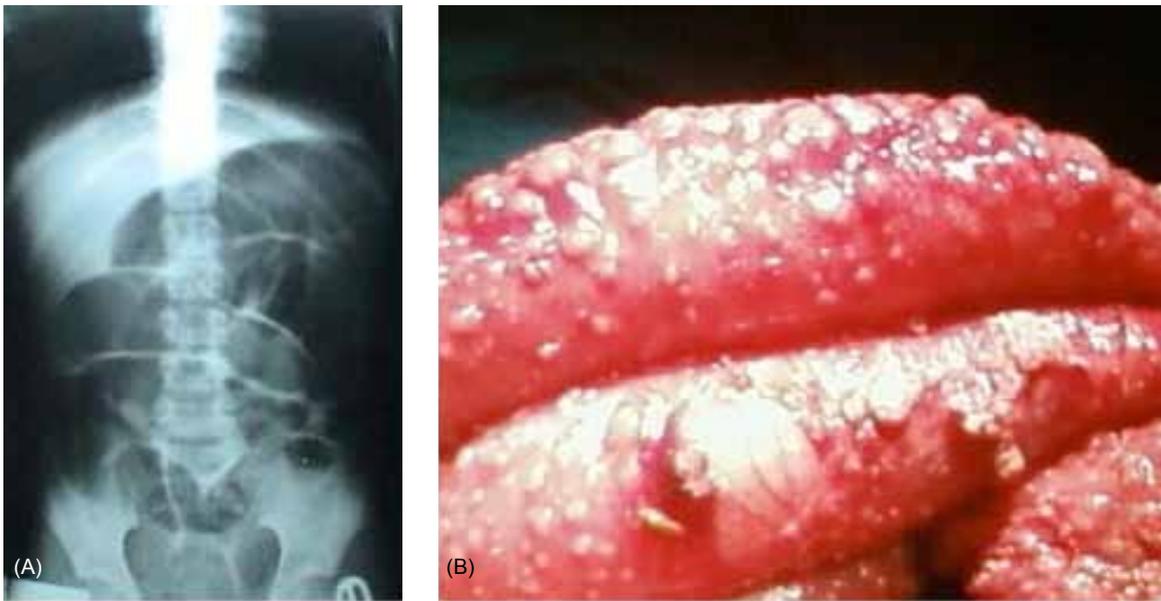
- airway obstruction, extrinsic lymph node compression or intraluminal obstruction;
- progressive primary infection-cavity formation;
- posttuberculous bronchiectasis;
- bronchial stenosis/stricture;
- drainage of lung abscess;
- bronchopleural fistula, broncho-oesophageal fistula;
- massive haemoptysis;
- chest wall sinus;
- posttubular constrictive pericarditis;
- fibrothorax/trapped lung;
- suspicion of malignancy;
- pulmonary resection for MDR-TB;
- tubercular rib osteomyelitis; and
- tubercular empyema.

Indications for pulmonary resection in cases of tuberculosis include:

- persistently positive sputum cultures with cavitation after 6 months of continuous optimal chemotherapy with two or more drugs;
- symptomatic bronchiectasis not controlled with conservative measures;
- advanced disease with extensive caseation necrosis;
- massive life-threatening haemoptysis or recurrent severe haemoptysis;
- trapped lung;
- localised disease with resistant organisms (localised disease defined as that encompassing one or two segments of the lung); and
- a mass lesion of the lung in an area of tubercular involvement.

### Surgery for Abdominal Tuberculosis

In GI tuberculosis, if symptoms recur after starting drugs, then elective surgery is planned. Emergency surgery may be required in 25–30% of abdominal tuberculosis cases, particularly those who present with perforation, acute intestinal obstruction not responding to conservative measures, acute peritonitis, and, rarely, significant hematochezia (Figure 18.2). Historically, bypassing the stenosed segment was practiced when effective antitubercular drugs were not available, as any surgery involved with side-to-side anastomosis or the resection of the bowel segment was considered hazardous in the presence of active disease. This practice, however, produced blind loop syndrome, fistulas, and recurrent obstruction in the remaining segments. With the advent



**Figure 18.2:** (A) X-ray of the abdomen of an 8-year-old boy showing multiple dilated loops of the bowel. The patient presented with distended abdomen, fever, vomiting, and constipation, with similar episodes reported in the past 6 months. (B) Operative findings of 8-year-old patient showing dilated loops of the bowel with multiple caseous granulomas involving the whole intestine. The seromuscular coat was quite inflamed and friable. There was a mass at the ileocaecal junction entrapping the bowel loops, resulting in an acute intestinal obstruction. Adhesionolysis, resection of the mass, and a double-barrel proximal ileostomy were done. Primary anastomosis was avoided because the bowel looked fiery and friable with active tubercular infection (child had not received antitubercular drugs).

of antitubercular drugs, more radical procedures became popular in an attempt to eradicate the disease locally. These procedures were not tolerated well earlier by the malnourished patient. Moreover, the lesions are often widely spaced and not suitable for resection. The abdomen is closed without drainage even in the presence of ascites or peritonitis.

The recommended surgical procedures today are conservative. A period of preoperative drug therapy is controversial; however, 2 weeks of multidrug therapy is considered minimal to reduce the chances of spread of active infection during surgery. Strictures that reduce the lumen by half or more and cause proximal hypertrophy or dilation are treated by strictureplasty. This involves an incision along the antimesenteric side, which is closed transversely in two layers. A segment of bowel bearing multiple strictures or a single long tubular stricture may merit resection, with a 5-cm safe margin. Tubercular perforations are usually ileal and are associated with distal strictures. Resection and anastomosis are preferred because simple closure of the perforation is associated with a high incidence of leakage and fistula formation and thus higher mortality.<sup>35</sup> For ileocaecal tuberculosis, limited resection of the ileocaecal area, rather than formal right hemicolectomy, involves lesser dissection and thus less chance of injury to the duodenum or ureter. For colonic lesions, resection is advocated.

Some obstructing intestinal lesions may also be relieved with antitubercular drugs alone without surgery. The mean time required for the relief of obstructive symptoms is usually 6 months.

Emergency surgery for intestinal obstruction is best avoided, as it carries 18–24% mortality. Thus, every patient who presents with intestinal obstruction should initially be managed conservatively. Tubercular perforations carry high mortality despite surgery. In contrast, elective surgery for GI tuberculosis carries only 0.5–2% mortality. Despite the advent of newer antitubercular drugs, abdominal tuberculosis carries a mortality of 4–12%. This is largely due to associated problems of malnutrition, anaemia, hypoalbuminaemia, and poor wound healing.

### Extrapulmonary Tuberculosis

Most cases of extrapulmonary TB, including cervical lymphadenopathy, can be treated with the same regimens used to treat pulmonary TB. Exceptions include bone and joint disease, miliary disease, and men-

ingitis. For these, the recommendation is a 2-month therapy of INH, rifampin, pyrazinamide, and streptomycin once a day, followed by 7–10 months of INH and rifampin once a day.

The other recommended regimen is 2 months of the same four drugs—INH, rifampin, pyrazinamide, and streptomycin—followed by 7–10 months of INH and rifampin twice a week. Capreomycin or kanamycin may be given instead of streptomycin in areas where resistance to streptomycin is common.

### Tuberculosis and HIV

The use of a regimen that uses rifabutin instead of rifampin has been advised when treating HIV disease and TB simultaneously.

The treatment regimen for TB initially should include at least three drugs and should be continued for at least 9 months. INH, rifampin, and pyrazinamide with or without ethambutol or streptomycin should be administered for the first 2 months. Treatment of disseminated disease or drug-resistant TB may require the addition of a fourth drug.

The tuberculin skin test, or Mantoux test, which is the standard marker of *Mycobacterium tuberculosis* infection in immunocompetent children, has poor sensitivity when used in HIV-infected children.<sup>9</sup> Novel T cell assays may offer higher sensitivity and specificity, but these tests still fail to make the crucial distinction between latent *M. tuberculosis* infection and active disease, and they are limited by cost considerations.<sup>9</sup>

Symptom-based diagnostic approaches are less helpful in HIV-infected children, as TB-related symptoms cannot be differentiated from those caused by other HIV-associated conditions. HIV-infected children are at increased risk of developing active disease after TB exposure/infection, which justifies the use of INH preventive therapy once active TB has been excluded.<sup>9</sup> HIV-infected children should also receive appropriate supportive care, including cotrimoxazole prophylaxis, and antiretroviral therapy, if indicated.<sup>9</sup> The management of children with TB/HIV infection could thus be vastly improved by better implementation of readily available interventions.

### Multidrug-Resistant Tuberculosis

Primary resistance is resistance to anti-TB treatment in an individual who has no history of prior treatment. Secondary resistance involves the emergence of resistance during the course of ineffectual anti-TB therapy.

Risk factors for the development of primary drug resistance include patient contact with drug-resistant contagious TB, residence in areas with a high prevalence of drug-resistant *M. tuberculosis*, HIV infection, and the use of intravenous drugs. Secondary drug resistance reflects noncompliance to the regimen, inappropriate drug regimens, and/or interference with absorption of the drug.

The current guidelines are that if a child is at risk or has disease resistant to INH, at least two drugs to which the isolate is sensitive on culture should be administered. Another principle is to never add a single drug to an already failing regimen. The resistance pattern, toxicities of the drugs, and the patient's response to treatment should determine the duration and regimen selected.

The initial treatment regimen for patients with MDR-TB should include four drugs. At least two bactericidal drugs (e.g., INH, rifampin), pyrazinamide, and either streptomycin or another aminoglycoside (also bactericidal) or high-dose ethambutol (25 mg/kg/d) also should be incorporated into the regimen.

Six-month treatment regimens and intermittent therapy are not advocated for patients with strains resistant to INH or rifampin.

In isolated INH resistance, the four-drug, 6-month regimen is started initially for the treatment of pulmonary TB. INH is discontinued when resistance is documented, but pyrazinamide is continued for the entire 6-month course of treatment.

In the 9-month regimen, INH is discontinued upon the documentation of isolated INH resistance. If ethambutol was included in the initial regimen, treatment continues with rifampin and ethambutol for a minimum of 12 months. If ethambutol was not included, then sensitivity tests are repeated, INH is discontinued, and two new drugs (e.g., ethambutol and pyrazinamide) are added.

Resistance to both INH and rifampin is a complicated issue. The initial drug regimen is continued (with two drugs to which the organism is susceptible) until bacteriologic sputum conversion is documented, followed by at least 12 months of two-drug therapy. The role of new agents such as quinolone derivatives and amikacin in MDR cases remains unclear.

Default from treatment was observed to be a major challenge in the treatment of MDR-TB due to long duration and the expense of ATT.<sup>36</sup>

### Monitoring for Side Effects

Adverse effects of INH (e.g., hepatitis) are rare in children; therefore, routine determination of serum aminotransferase levels is not necessary. Monthly monitoring of hepatic function tests may be done for patients with severe or disseminated TB, miliary TB, concurrent or recent hepatic disease, or clinical evidence of hepatotoxic effects, and for those receiving high daily doses of INH (10 mg/kg/d) in combination with rifampin, pyrazinamide, or both. In the rare case when the patient has symptoms of hepatitis, the regimen is discontinued and liver function is evaluated. If the tests are normal or return to normal, then a decision to restart the medications may be made. The drugs are reintroduced one by one.

### Follow-up

A regular follow-up every 4–8 weeks is done to ensure compliance and to monitor the adverse effects of and response to the medications administered. The weight of the child is measured at each visit. The sclera is examined for any evidence of jaundice.

Follow-up ESR and chest x-ray (CXR) may be obtained after 2–3 months of therapy to observe the response to treatment in patients with pulmonary TB. However, hilar lymphadenopathy may take several years to resolve. Thus, a normal CXR is not required for termination of therapy.

## Complications

### Complications of Chest Tuberculosis

Complications of chest tuberculosis include:

- miliary tuberculosis;
- tubercular meningitis;
- pleural effusion;
- pneumothorax;
- complete obstruction of a bronchus if caseous material extrudes into the lumen;
- atelectasis;
- bronchiectasis;
- stenosis of the airways;
- broncho-oesophageal fistula; and
- endobronchial disease.

### Complications of Abdominal Tuberculosis

Complications of abdominal tuberculosis include:

- subacute intestinal obstruction;
- adhesions;
- intestinal stricture;
- malabsorption; and
- short bowel syndrome.

## Prevention

BCG vaccine is given at birth to all newborns in developing countries where tuberculosis is endemic.

The best method to prevent cases of paediatric tuberculosis is to find, diagnose, and treat cases of active tuberculosis among adults. Children do not usually contract tuberculosis from other children or transmit it themselves. Adults pass tuberculosis on to children. Improved contact investigations and use of directly observed therapy should increase the success rate of finding and treating adult cases of tuberculosis, therefore reducing the number of cases of paediatric tuberculosis.

Mothers infected with tuberculosis (but under regular treatment) should remain away from their babies until their sputum is negative. This is usually after 2 months of a four-drug regimen given to adults. During this period, mothers do not feed their babies directly, but the breast milk is expressed and then boiled before being fed to the baby, despite of the fact that this has the risk of destroying the nutrients. The baby is also given prophylactic INH therapy, 5 mg/kg daily for 6 months. The baby is immunised with INH-resistant BCG vaccine soon after birth.

## Prognosis

The prognosis varies according to the clinical manifestation. A poor prognosis is associated with disseminated TB, miliary disease, and tubercular meningitis. Higher mortality rates (20%) occur in children <5 years of age.

## Key Summary Points

The new WHO Stop TB Strategy, released in 2006, has identified six principal components to reduce the global burden of TB by 2015:

1. Pursue high-quality DOT expansion and enhancement.
2. Address TB/HIV, MDR-TB, and other challenges.
3. Contribute to health system strengthening.
4. Engage all care providers.
5. Empower patients and communities.
6. Enable and promote research.

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