Alper Sener · Hakan Erdem *Editors*

Extrapulmonary Tuberculosis

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Chapter 1
Epidemiology of Extrapulmonary Tuberculosis

Ekaterina Kulchavenya, Kurt G. Naber, and Truls Erik Bjerklund Johansen

1.1 Introduction

Tuberculosis (TB) remains one of the world's deadliest communicable diseases and is regarded a major global health problem. In 2012, an estimated 8.6 million people developed TB, and 1.3 million died from the disease (including 320,000 deaths among HIV-positive people). In 2013, an estimated 9.0 million people developed TB, and 1.5 million died from the disease, 360,000 of whom were human immunodeficiency virus (HIV)-positive. In 2014, TB again killed 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive). Worldwide, 9.6 million people were estimated to have fallen ill with TB in 2014: 5.4 million men, 3.2 million women, and 1.0 million children. Globally, 12% of the 9.6 million new TB cases in 2014 were HIV-positive. Thus, there is a negative trend with increased incidence from 8.6 million people to 9.6 million people and mortality – from 1.3 million to 1.5 million during 3 years (from 2012 until 2014) [1–4]. Given that most deaths from TB are preventable, the death toll from the disease is unacceptably high.

TB is a multisystem disease with a myriad of presentations and manifestations; it can affect almost any organ or tissue, excluding only hair and nails. While the WHO has recognized TB as a global problem, this applies to TB as a whole and especially to pulmonary TB (PTB). TB in general has not only medical but also

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great social importance as extrapulmonary TB (EPTB) is one of the most common reasons for both male and female infertility, especially in endemic regions, and in some studies, sexual transmission of TB has also been described [5–7].

1.2 Epidemiology of Extrapulmonary Tuberculosis

Over the last decades, extrapulmonary locations of the disease have become more frequent. This is thought to be due to the increased prevalence of acquired immune deficiency syndrome and the increased number of organ transplants [8, 9]. Although extrapulmonary tuberculosis (EPTB) is less frequent than PTB and is a secondary target for national TB control programs, its significance has increased worldwide during the HIV epidemic [10]. The proportion of EPTB varies according to geographical region, comorbidity, presenting symptoms, epidemic situation, time period, etc. The most commonly affected sites of EPTB in Korea were pleura, followed by lymph nodes. Gastrointestinal organs, bones and joints, the central nervous system, and urogenital TB (UGTB) were the least common sites [11].

In Bangladesh EPTB constitutes about 15–20% of all cases of TB patients, and it is more common in low socioeconomic groups (60%). The incidence of EPTB was as high as 55% in the age group 16–45 years (mean age 35.67 ± 14.6 years) where female patients accounted for 60% of cases [12]. The rate of EPTB in Brazil increased from 6.8 per 100,000 people in 1981 to 7.0 per 100,000 people in 1991. In the period between 2001 and 2009, a 23.7% reduction was seen in the number of PTB cases, but only a 5.9% reduction in the number of cases of EPTB was found [10].

EPTB constitutes 15–20% of tuberculosis cases in India. The outcome of directly observed treatment short-course treatment of EPTB has been evaluated in 2219 patients. There were more males in the age group 15–45 years. Overall treatment completion rate was 84% in EPTB patients. Treatment completion rate was 66% in HIV-positive patients compared to 86% in HIV-negative EPTB patients. Individually, observed treatment completion rates were as follows: lymph node TB 90.9%, UGTB 92.6%, bone and joint TB 86%, pleural effusion TB 84.7%, abdominal TB 76%, and central nervous system (CNS) TB (tuberculoma and meningitis) 63.7%. The site of EPTB was not recorded in 173 (7.8%) patients [13].

In most cases, EPTB occurs in immunosuppressed patients as part of a severe illness due to hematogenous spread. In some regions authors have found that extrathoracic involvement most often means abdominal organs and the urogenital tract and less commonly the central nervous system (CNS) and the musculoskeletal system. Most frequently, computed tomography (CT) is used for detecting extrathoracic TB manifestations, except for CNS and musculoskeletal manifestations, where contrast-enhanced magnetic resonance imaging (MRI) is the gold standard. Due to unspecific symptoms, the diagnosis is often delayed [14].

Among 253,299 cases, reported from 1993 to 2006 in the United States, 73.6% were PTB, and 18.7% were EPTB, including lymphatic (40.4%), pleural (19.8%),

bone and/or joint (11.3%), genitourinary (6.5%), meningeal (5.4%), peritoneal (4.9%), and unclassified EPTB (11.8%) cases. Compared with PTB, EPTB was associated with female sex and foreign birth, almost equally associated with HIV status, and negatively associated with multidrug resistance and several tuberculosis risk factors, especially homelessness and excess alcohol use [15].

Among a total of 427,548 TB cases, 57,217 (13.4%) were EPTB in Brazil, and 13,989 (3.3%) were concurrent pulmonary and extrapulmonary TB. Patients with EPTB were mainly white (16.7%), and most patients (29.1%) had 5–8 years of education. Among comorbidities, HIV infection was prominent. Ethanol abuse, diabetes mellitus, and mental illness were associated with PTB, but not with EPTB [10].

The spectrum of EPTB in Brazil is shown in Fig. 1.1.

In Brazil, although EPTB primarily affects adults, one-fourth of all cases of EPTB occurred in children less than 14 years of age [10].

For comparison we show the spectrum of EPTB in Siberia in Fig. 1.2 over the years 1999–2011 [16]. The percentage of UGTB went down, and the bone and joint TB went up, in 2011 both representing about one-third of EPTB.

Tuberculosis is a very common disease in Bangladesh. A retrospective histopathological study was performed to assess the distribution of extrapulmonary tuberculosis (EPTB) in various organs by examination of 216 biopsy specimens. The majority of cases were females (126). Lymph nodes were the most common site of EPTB (62.9%) followed by the skin and subcutaneous tissue (17.59%), intestine (11.11%), breast (2.77%), female genital tract (2.31%), male genital tract (1.38%), and bone and joint (1.85%). Out of 136 cases of tubercular lymphadenitis, 96 (70.58%) were cervical, 18 (13.23%) were axillary, 12 (3.82%) were mesenteric, and 10 (7.35%) were inguinal. Cervical lymph nodes are very common sites for EPTB [17].

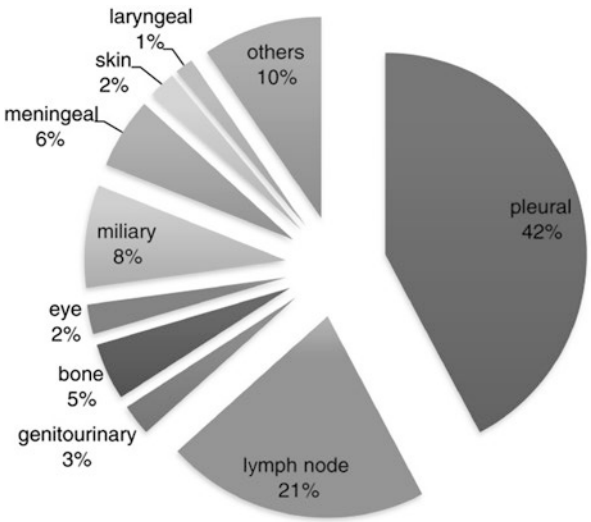

Fig. 1.1 Spectrum of EPTB in Brazil [10]

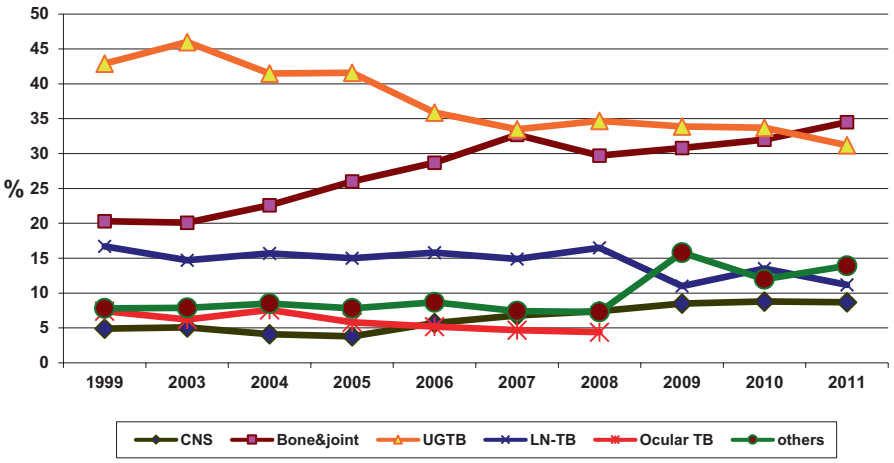

Fig. 1.2 Spectrum of EPTB in Siberia [16]. Annotation: CNS, TB of the central nervous system; bone and joint, TB of the bone and joints; UGTB, urogenital TB; LN-TB, lymphonodal TB

Table 1.1 Percentage of EPTB among all forms of TB in various countries

Country	% of EPTB	Reference
Bangladesh	20	[15]
India	15–20	[16]
Brazil	13.4	[7]
Poland	5.7	[24]

Purely EPTB was diagnosed in 415 patients in Poland in 2013 (5.7% of all registered cases). Most patients had pleural TB (142 cases) followed by peripheral lymph node TB (104 cases), UGTB (58 cases), and bone and joint TB (44 cases) [18].

The percentage of EPTB among all forms of TB is shown in the Table 1.1.

Tables comparing spectra of EPTB can be misleading, as classification of EPTB varies from country to country. In some regions, for example, in Brazil, miliary TB is considered EPTB, although in fact it is not only EPTB but a totally generalized TB. In some countries pleural TB and laryngeal TB are considered EPTB and in others PTB. Some countries count only isolated EPTB as such; others count also EPTB in combination with PTB. Some countries count abdominal TB, skin TB, etc., separately; some classify these forms together as "others." Although the true epidemiological figures of EPTB may be incomplete due to diagnostic problems and different statistical reports, the medical and social importance of EPTB remains undoubted.

1.3 Urogenital Tuberculosis (UGTB)

UGTB is defined as an infectious inflammation of the urogenital system and its organs in any combination, caused by *Mycobacterium tuberculosis* (Mtb) or *M. bovis*. By definition it includes both urological and gynecological TB (female genital TB) [16, 19, 20].

UGTB is one of the most frequent forms of EPTB. UGTB is the fourth most common manifestation of extrapulmonary TB, but it is often underdiagnosed by clinicians because of few and non-specific symptoms and insidious disease courses [21]. Authors from North America considered UGTB even as the third most common form of EPTB after pleural TB and lymphatic TB [22].

Starting with a pulmonary focus, 2–20% of patients develop UGTB through hematogenous spread to the kidneys, prostate, and epididymis; through the descending collecting system to the ureters, bladder, and urethra; and through the ejaculatory ducts to the genital organs. In Brazil UGTB occurs at all ages, but it is predominant in males in their fourth and fifth decades. In other countries the sex-age proportions may be different [23]. UGTB is a serious, insidious disease, generally developing symptoms only at a late stage, which leads to diagnostic delay with the consequence of urogenital organ destruction. There are reports of patients with renal failure as their initial clinical presentation. Figueiredo et al. noted that although the condition has been long recognized by nephrologists, urologists, and infectious disease specialists, UGTB is still largely unknown by other physicians [23].

In the pre-antibacterial era the prevalence of UGTB was higher: every fifth urological inpatient had UGTB, and more than a third of all pyonephrosis cases was due to TB. In that period, UGTB patients were mostly young people, equally male and female [23]. Now UGTB is the most common form of EPTB in countries with epidemic TB, but in countries with low incidence rates, UGTB is rarer [22, 25]. In developed countries, urogenital manifestations are responsible for over 40% of extrapulmonary cases [26]. In Europe UGTB is diagnosed more often in migrants than in the native population [27]. Renal involvement in TB infection is underdiagnosed in most health-care centers, and it can be a part of a disseminated infection as well as a localized urogenital disease [8]. This disease should be suspected in patients with unexplained urinary tract infections, especially in immunocompromised patients and/or in patients coming from endemic areas [8].

Today the proportion of UGTB among all extrapulmonary forms of TB varies depending on region, epidemic situation, comorbidity, awareness of doctors and population, time period, etc. Some authors consider UGTB to be the third most common form of EPTB accounting for 15–20% and even 40% of EPTB cases [22, 25, 26], while other authors report about 4–17% only [8, 25, 26].

In Italy UGTB represents about 27% of all extrapulmonary localizations of TB and may be due either to a disseminated infection or to a primary urogenital localization [9]. Although UGTB is one of the most common forms of EPTB in countries with epidemic TB, the proportion of UGTB is lower in countries with low incidence rates of TB [16, 19, 20]. UGTB was lowest among all extrapulmonary sites in Korea

[11]. Of 135 patients with extrapulmonary TB diagnosed in Korea between 2006 and 2013, only 6 (4.4%) had UGTB [28]. Among 415 Polish patients diagnosed with extrapulmonary TB, 58 (14.0%) had UGTB [18]. In Turkey UGTB was diagnosed in 5.4% of all extrapulmonary sites [29]. Surprisingly, in Bangladesh the proportion of UGTB was also low [12]. Proportion of UGTB among EPTB is shown in Table 1.2.

UGTB is often underestimated by clinicians because of few and non-specific symptoms and insidious disease courses. Reported statistics may therefore be falsely low [19].

The occurrence of UGTB in the Siberian and Far Eastern Federal Districts of Russia was analyzed for the period 1999–2015. The highest proportion of UGTB among EPTB was found in 2003 (46%), the lowest in 2014 (22.9%). According to outpatient medical records, the proportions of patients with stage 1, stage 2, and cavernous forms of nephrotuberculosis ranged from 21.2% to 37%, 26% to 53.5%, and 21.6% to 37%, respectively. The incidence of prostate tuberculosis ranged from 0 in 2003 and 7.1% in 2008 to 54.2% in 2013, with an average of 33.9% [30].

Currently, it is impossible to estimate the true incidence of UGTB in eastern Russia. Every fourth UGTB patient was under medical evaluation with a wrong diagnosis for 5 or more years. Introduction of new technologies has led to an improvement of bacteriological verification of UGT and increased prostate tuberculosis detection rate to 35.7% of all cases of UGTB [30].

After screening 1036 cases of suspected urinary tuberculosis (UTB) during 2009 to 2014, 193 patients with UTB were enrolled to investigate the epidemiology, clinical features, and drug-resistance profile. The most common presenting symptoms were urinary irritation (61.1%) and lumbago (49.2%). There were high proportions of microscopic hematuria (63.2%) and microscopic proteinuria (45.6%). The positive rate for TB-DNA in urine was 66.3%. The positive rate for culture was 13.1%, and for smear it was 9.8% only. The total rate of drug-resistant Mtb (resistant to at least 1 drug) was 39.7%, of which 20.7% was multidrug-resistant Mtb (resistant to at least rifampicin and isoniazid simultaneously). Molecular diagnostics is crucial for the definite diagnosis of UGTB. Real-time polymerase chain reaction for TB-DNA identification instead of culture and genotype tests for estimation of drug resistance of Mtb is recommended as routine assays for patients with suspected UGTB [31].

To estimate the prevalence and spectrum of kidney TB (KTB) in children and teenagers in an epidemic region, the histories of 131 patients with UGTB in Siberia and 819 patients with UGTB in Kyrgyzstan were reviewed [32]. In Siberia only two

Table 1.2 Proportion of UGTB among EPTB in various countries

Country	% of UGTB among all EPTB	Reference
Italy	27.0	[21]
Korea	4.4	[23]
Poland	14.0	[24]
Turkey	5.4	[25]
Siberia	22.9–46.0	[26]

children and one teenager with UGTB were found (2.3% of the cohort of UGTB); all had KTB stage 1. In Kyrgyzstan 17 children and 21 teenagers were diagnosed with UGTB (4.6% of all UGTB patients). All had a long history and had undergone surgical interventions, six had fistulae, and two teenagers had microcystis (bladder TB stage 4). KTB stage 1 was diagnosed in two children only, KTB stage 2 in four patients, KTB stage 3 in eight, and KTB stage 4 in three children. Thus, 64.5% of patients were diagnosed in a late and complicated stage [32].

UGTB may be due either to a disseminated infection or to a primary urogenital localization [8]. Renal involvement in TB can be part of a disseminated infection or a localized genitourinary disease [9]. Awareness of renal TB is urgently needed by physicians for suspecting this disease in patients with unexplained urinary tract abnormalities, mainly in those with immunosuppression and those coming from TB-endemic areas [9].

The risk of TB is significantly increased in chronic kidney disease [33]. The link between chronic kidney disease and TB has been known for more than 40 years, but the interaction between these two diseases is still poorly understood. Dialysis and renal transplant patients appear to be at a higher risk of TB, in part related to immunosuppression along with socioeconomic, demographic, and comorbid factors [34–36].

1.4 Lymph Node Tuberculosis

The appearance of enlarged lymph nodes in granulomatous diseases, such as TB and sarcoidosis, can be very similar to that of metastatic lymph nodes or lymphomas, and ultrasound is commonly used in the early diagnostic evaluation. Anechoic or hypoechoic areas in a lymph node can represent necrosis or metastatic hemorrhages but also suppuration in inflamed lymph nodes. Patients diagnosed with lymph node abnormalities may be referred for ultrasound-guided targeted fine-needle aspiration biopsy or a lymph node extirpation for histopathological examination and final diagnosis [37].

In Bangladesh lymph nodes are the most common site of involvement (50%) [12]. In India the commonest sites of EPTB were also lymph nodes (34.4%), as well as in Turkey (39.4%) [28]. Lymph node involvement was more common in females (58%) [13].

The diagnostic value of interferon-gamma release assays (IGRA) in TB varies a lot with different sites of infections, with higher sensitivity in chronic forms of TB such as lymph node TB. IGRA exhibits high diagnostic accuracy in TB lymphadenitis. The diagnostic value of IGRA differs by different IGRA methods, ethnicity, and lymphadenitis location. The technology is more applicable in TB prevalent areas [38].

1.5 Tuberculosis of the Central Nervous System

TB of the central nervous system (CNS-TB) is the most severe form of TB and is often associated with high mortality [39]. Serious complications such as rupture of intracranial tuberculous aneurysms are described [40].

CNS-TB takes three clinical forms: meningitis (MTB), intracranial tuberculoma, and spinal arachnoiditis. MTB predominates in the Western world and presents as a subacute to chronic meningitis syndrome with a prodrome of malaise, fever, and headache progressing to altered mentation and focal neurologic signs, followed by stupor, coma, and death within 5–8 weeks of onset. Vasculitis leading to infarcts in the basal ganglia occurs commonly and is a major determinant of morbidity and mortality. CNS-TB commonly manifests itself as tubercular meningitis. CNS tuberculomas are more commonly seen intracranially and less frequently involve the spinal cord. Combination of intramedullary and intracranial tuberculoma is extremely rare. However, magnetic resonance imaging (MRI) of the brain should still be performed in all cases of intramedullary spinal tuberculoma because of the possible presence of early asymptomatic/mild symptomatic intracranial tuberculomas [41, 42].

In India, about 1000 patients die daily due to CNS-TB, according to the Tuberculosis Control Society of India. CNS-TB causes considerable morbidity and mortality in rural young adults resulting in severe loss of manpower [42]. According to other Indian reports, 9.4% of all EPTB patients had TB lesions in the CNS [13, 43].

Ninety-three patients (38.7% females and 61.3% males) were enrolled in a prospective study for evaluation of clinical and radiological findings in patients with intracranial tuberculosis in Northeast India. Alcohol abuse was the most common risk factor seen in 19.4%. Headache was the most common symptom (90.3%). Coinfection with human immunodeficiency virus, cryptococcal infection, and toxoplasmosis were seen in 11, 3, and 2 patients, respectively. Cerebrospinal fluid analysis showed acid-fast bacilli in one patient; polymerase chain reaction for TB and BACTEC was positive in one and three patients, respectively. BACTEC MGIT 960 system, a fully automated and nonradiometric culture system, has been recommended for faster mycobacterial isolation from clinical specimens. Neuroimaging showed basal exudates (21.7%), tuberculoma (28.6%), brain edema (27%), hydrocephalus (32.9%), infarction (21%), and abscess (2.9%). A total of 25 patients (26.9%) died, and 38 patients (40.9%) developed neurological sequelae like hemiparesis, paraparesis, visual loss, and hearing loss [44].

Central nervous system involvement is rather rare in Morocco but is seen in the context of multifocal or miliary tuberculosis. CNS-TB may be seen also in immunocompetent subjects. Active assessment of associated extracerebral tuberculous infection has a big role in cases of cerebromeningeal lesions suggestive of tuberculosis [45].

CNS-TB is becoming more and more complex and atypical with onset of multidrug-resistant TB. Routine diagnostic techniques using serology Mantoux test are time-consuming and may delay the definitive management. Hence, it is important

to be familiar with various radiologic features of CNS-TB to ensure early and accurate diagnosis, thereby reducing the high morbidity and mortality associated with the disease. The newer imaging techniques such as MRI further help to improve the characterization and diagnosis of atypical CNS-TB [46].

1.6 Bone and Joint Tuberculosis

Spinal TB, also known as Pott disease, was first reported by Percivall Pott in 1779. One of the most common extrapulmonary forms of TB, spinal TB, accounts for 50–60% of osteoarticular TB. The onset of spinal TB is insidious, usually manifesting first as back pain and local tenderness as well as some systemic symptoms associated with TB. Spinal kyphotic deformity and neurological symptoms may occur in later stages [47].

TB is a major health problem in the developing world. One-third of children infected with *Mycobacterium tuberculosis* have extra pulmonary involvement. Skeletal TB occurs in 1–6% of them with vertebra being the commonest site in India. Pure tubercular osteomyelitis without joint involvement occurs in only 2–3% of cases of osteoarticular tuberculosis. Common sites are the femur, tibia, and fibula. Disseminated skeletal involvement is very rare in children (7%), and calvarial osteomyelitis is even rarer (1%) [48].

Musculoskeletal TB accounts for approximately 10% of all EPTB cases in the United States and is the third most common site of EPTB after pleural and lymphatic disease. Vertebral involvement (tuberculous spondylitis, or Pott's disease) is the most common type of skeletal TB, accounting for about half of all cases of musculoskeletal TB. Concomitant pulmonary involvement may not be present, thus confusing the diagnosis even further [49].

TB has become increasingly widespread in China. Bone and joint tuberculosis (BJTB) constitutes about 10% of total EP TB cases, and spinal tuberculosis is known as the most common site among skeletal tuberculosis (about 44%) [50]. Other authors in China think that osteoarticular tuberculosis accounts for only 1–2% of all cases of TB [51].

The musculoskeletal system is involved in about 20% of patients diagnosed with tuberculosis in Turkey. Although musculoskeletal tuberculosis generally affects the spine and large joints (hip and knee), hand involvement is seen in 10% of the patients with musculoskeletal TB, while isolated tuberculosis of the hand or wrist is much more rare [52]. Other authors have found the bone TB in 7.4% of EPTB involvement in Turkey [28].

Another rare localization of skeletal TB was described by Grover et al. They reported a case of tubercular infection of the sternum located in the xiphoid process resulting in its presentation as an epigastric swelling. Multi-sliced computed tomography and MRI demonstrated erosive osteomyelitis of the xiphoid process with enhancing inflammation in the adjoining soft tissue. Ultrasound-guided aspiration, PCR, and amplified *Mycobacterium tuberculosis* DNA test confirmed tubercular infection [53].

1.7 Abdominal Tuberculosis

TB affecting the gastrointestinal tract was recognized as early as the fourth century BC in texts by Hippocrates. While TB of the gastrointestinal tract is not as common as pulmonary TB, it is an important cause for TB-related morbidity and mortality. The pathogenesis of this form of tuberculosis involves spread of mycobacteria to the gastrointestinal tract by a number of ways: hematogenous spread, swallowing of sputum contaminated with live *M. tuberculosis*, ingestion of contaminated food, or direct spread from adjacent organs [54]. Microbiologic confirmation of TB is possible in 40% of intestinal tuberculosis cases in children [55].

Gastrointestinal tuberculosis may mimic malignancy, especially in the elderly. Lakhe et al. presented a 46-year-old female patient with a 6 month's history of diffuse pain in the abdomen with low-grade fever and loss of weight and appetite. Computerized tomography revealed a diffuse concentric long segmental thickening of the terminal ileum, ileocecal junction, ascending colon, and narrowing of the splenic flexure of colon suggesting an infective etiology. Colonoscopy showed an ulcero-nodular lesion at the splenic flexure raising the possibility of colonic cancer and thickening of the ascending colon and cecum. Biopsy smear showed occasional acid-fast bacilli (AFBs), and mycobacterium tuberculosis could be detected by GeneXpert [56]. A case of penetrating gastric ulcer as a manifestation of multisystemic TB has also been described [57].

Abdominal TB is an uncommon entity in the United States. Colonic TB is reported in 2–3% of patients with abdominal TB. It is frequently misdiagnosed as Crohn's disease or carcinoma of the colon due to their shared clinical, radiographic, and endoscopic presentations [54]. In India abdominal TB was diagnosed in 12.8% of EPTB patients [13].

An endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was performed in a patient presenting with an asymptomatic peripancreatic mass-like lesion. Polymerase chain reaction (PCR) using tissue obtained via EUS-FNA showed that the peripancreatic mass-like lesion was also positive for tuberculosis. Authors emphasized that in patients with enlarged lymph nodes, including those in the abdominal area, tuberculous lymphadenitis is a potential diagnosis [58].

1.8 Treatment Outcome of EPTB

Treatment outcome of EPTB was poor in HIV-infected patients and in those with CNS-TB [13]. Treatment is most effective when started in the early stages of disease and should be initiated promptly in case of strong clinical suspicion without waiting for laboratory confirmation. The initial four-drug regimen (isoniazid, rifampin, pyrazinamide, ethambutol) covers the possibility of infection with a resistant strain, maximizes antimicrobial impact, and reduces the likelihood of emerging resistance during therapy. Adjunctive corticosteroid therapy has been shown to reduce morbidity and mortality in all but late-stage disease [13, 49].

A new nanocarrier prepared by nanoprecipitation has been developed for the passage of gatifloxacin through the blood-brain barrier to treat central nervous system tuberculosis [59].

1.9 Conclusion

EPTB is a "great imitator." As this disease is multisystemic with a myriad of presentations and manifestations, high awareness of physicians is important. TB should be suspected in all patients with an unusual course of any disease where standard therapy has low efficiency. Comparison of EPTB spectra is very difficult, as classification of EPTB varies from country to country. Some countries count isolated EPTB, while others also count EPTB in combination with PTB. Nevertheless, EPTB with all its subgroups has great medical and social importance.

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Chapter 2
Pleural Tuberculosis

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2.1 Introduction

Tuberculosis is still among the most deadly illnesses worldwide. Tuberculosis primarily affects the lungs, but it may involve almost every organ and tissue. Pleura is a membrane consisting of two parts as visceral and parietal pleura which surrounds and separates the lungs from the chest wall. Pleural tuberculosis or tuberculous pleural effusion is the second frequent form of extra-pulmonary tuberculosis in adults after lymphoid involvement. Pleural tuberculosis is also the most common cause of pleural effusions in tuberculosis endemic areas or developing countries and the fourth leading cause of pleural effusion after cancer, pneumonia, and heart failure in developed regions [1, 2]. Despite the global incidence of pulmonary tuberculosis has been reducing, the incidence of extra-pulmonary tuberculosis has increased due to HIV and increase of immunocompromised patients. Pleural tuberculosis may be a manifestation of primary tuberculosis or due to reactivation of pre-existing tuberculosis foci.

2.2 Epidemiology

According to the World Health Organization, tuberculosis is the ninth leading cause of death worldwide. It was estimated that tuberculosis caused to 1300, 000 deaths among HIV-negative people and 374, 000 deaths among HIV-positive people in 2016. New tuberculosis cases were estimated as 10.4 million people also [3]. Up to 30% of patients with tuberculosis have tuberculous pleural effusion (TPE) [4]. The incidence of pleural tuberculosis among patients with tuberculosis is changing from

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population to population and goes parallel with the epidemiology of tuberculosis. High percentages are seen in the tuberculosis burden countries such as Burundi, South Africa, Zimbabwe, Uganda, and Southeast Asia. Tuberculosis is the major cause of pulmonary effusion in developing countries, and the percentage of pleural tuberculosis may account up to 80% of pleural effusions [1, 2]. In these countries, pleural tuberculosis affects mainly younger patients. In the countries with the lower incidence, TPE develops as a result of reactivation of latent tuberculosis or pre-existing focus and more frequent among the elderly population. Human immunodeficiency virus infections and the use of immunosuppressive drugs have increased the incidence [5, 6].

2.3 Pathogenesis

Formerly, TPE was believed as a result of pure delayed-type hypersensitivity reaction to mycobacterial antigens because of not to be able to demonstrate *M. tuberculosis* from pleural fluid. Development of new and sensitive diagnostic tests changed the perspective to the pathogenesis of pleural tuberculosis. The results of molecular studies in recent years indicate simultaneous pleuro-pulmonary involvement. Pleural space might be involved by two mechanisms. First and the principal mechanism is the direct extension of subpleural caseous focus into the pleural space in the course of primary infection after exposure to *M. tuberculosis*. The second mechanism is that a pleural disease may develop via haematogenous spread following primary infection without apparent parenchymal involvement. A few microorganisms may enter to pleural space and mycobacteria and/or cellular wall antigens such as protein/proteoglycan complex and lipoarabinomannan and stimulate an immune response, which is resulted in a delayed-type hypersensitivity reaction in the presence of cell-mediated immunity. Neutrophils are the first responding cells followed by macrophages. Macrophages phagocytose mycobacteria, and present antigens to the T lymphocytes, following T lymphocytes become activated and promote differentiation of macrophages through cytokines such as interferongamma, interleukin-2. Activated macrophages produce tumour necrosis factor (TNF), interleukin-1. Both of them are involved in lymphocyte activation, and TNF is involved in granuloma formation [7]. An increase of pleural capillary permeability, cytokine- mediated inflammatory process, and obstruction of the lymphatics of the parietal pleura all lead to the pleural fluid formation, entry of serum proteins and accumulation of leucocytes, and then granuloma formation [8]. In other words, TPE is the result of pathological immune reactions. The post-primary form develops with reactivation of a pre-existing focus, after long periods of infection [9].

Rarely, tuberculous pleural effusion may progress to tuberculous empyema. Besides, at the existence of post-primary cavitary disease, via the rupture of a cavity or through the bronchopleural fistula, a large number of microorganisms may enter into the pleural space, and tuberculous empyema may develop. Tuberculous empyema is characterized by a purulent fluid containing intensive microorganisms and neutrophils.

2.4 Clinical Manifestations

Variation in clinical presentations can be seen in pulmonary tuberculosis due to mycobacteria load, immune status of the patient, size of pleural effusion, and pulmonary involvement. Pleural effusions may be small, medium-sized, large, or massive. Generally, pleurisy develops in 3–6 months after the primary infections and often causes no symptoms. It is unnoticed clinically and self-resolved, but there is a risk of recurrence later. Pleural involvement is unilateral (90%) in most of the cases. Bilateral involvement may be detected in 10% of patients [9, 10]. An acute or subacute illness emerged after primary infection with fever (85%), nonproductive cough (75%), pleuritic chest pain (70%), night sweats, constitutional symptoms, and rarely dyspnoea if the pleural effusion is large [11]. Attenuation of breath sounds and dullness to percussion might be detected on physical examination. This presentation is frequently seen in younger patients in endemic regions and may be confused with bacterial pneumonia with parapneumonic effusion. The manifestation of illness may be more insidious with the low-grade fever, weight loss, malaise, and night sweats in elderly and in immunocompromised patients, and it may be confused with other pulmonary diseases such as congestive heart failure, malignancy, pneumonia, or a pulmonary embolus. Additional signs and symptoms such as night sweats, diarrhoea, lymphadenopathy, and hepatosplenomegaly might be seen in HIV-infected patients. If pleural fibrosis and thickening have been developed, chronic chest pain and dyspnoea with constitutional symptoms are prominent symptoms, and impairment in lung function is also detected [9, 11].

2.5 Diagnosis

Tuberculous pleural effusion should be suspected in the patients with pleural effusion and compatible epidemiologic risk factors for tuberculosis such as prior history, tuberculosis exposure, family history, and living or travelling to a tuberculosis-endemic area. Definitive diagnosis of tuberculous pleural effusion is the demonstration of *M. tuberculosis* in sputum, pleural fluid, or pleural biopsy specimens. The histological demonstration of caseating or epithelioid cell granuloma together with acid-fast bacilli in pleura has also diagnostic value. The initial evaluation of patients with suspected TPE should include diagnostic evaluation for pulmonary tuberculosis, imaging studies, examination of sputum for acid-fast bacilli, tuberculosis culture, and/or nucleic acid amplification test if available [12]. The peripheral leukocyte count is usually within normal ranges.

The chest X-rays are the initial radiological exam, typically showing unilateral pleural effusion, more frequently in the right hemithorax. The bilateral disease occurs in less than 10% of cases. Approximately 20% of patients with TPE have coexisting lung parenchymal disease on the same side on chest radiograph. Diagnostic sensitivity of chest X-ray is very low; contrarily tuberculous empyema

is usually associated with remarkable pulmonary parenchymal disease on chest X-rays. High-resolution chest tomography is much more sensitive than X-ray to show the parenchymal abnormalities, and it can demonstrate coexisting pulmonary involvement (such as micro-nodules, interlobular septal thickening) in 40–85% of cases [13]. Thoracic ultrasound may give additional information about the nature of effusion and guide to the biopsy site [14].

Sputum acid-fast bacilli smear and *M. tuberculosis* culture may be positive even in the absence of parenchymal involvement. Sensitivity could be increased with induced samples. High positive results are obtained among HIV-infected patients [15, 16].

If there is a sufficient fluid, a diagnostic thoracentesis should be performed. The cell count-differentiation; cytological, biochemical (protein, glucose, pH, lactate dehydrogenase, and others), and microbiological tests (acid-fast bacilli smear and culture, Gram stain and culture, PCR, etc.); and adenosine deaminase (ADA) level (if the effusion is lymphocyte predominant) should be analysed in all pleural effusion samples. The normal pleural fluid has the following characteristics: appearance is clear; pH is between 7.60 and 7.64; white blood cells are <1000/mm^3; protein content is <50% of serum levels (1–2 g/dL); lactate dehydrogenase is <50% of serum levels; and glucose is similar to blood levels. According to Light's criteria, the tuberculous pleural effusion is an exudative, straw coloured appearance, it may be slightly bloody at some samples, and pH is less than 7.40. The white blood cell counts are in the range of 100–5000 cells/μL with lymphocytic predominance in 60–90% of cases, but polymorphonuclear leukocytes may predominate in early course of the disease. Eosinophilia is rare, and the presence of more than 10% eosinophils suggests an alternative diagnosis [17]. Atypical appearance such as purulent, chylous, and pseudochylous may be seen rarely, particularly in empyema [18]. The protein concentration of tuberculous pleural effusion is expected to be >3.0 g/dL and greater than 50% of the serum protein concentration, and high protein levels>5 g/dL may be detected. Glucose level may be normal to low. Lactate dehydrogenase levels may be elevated in approximately 75% of cases, with levels of >500 international units/L.

Because few organisms are present in the pleural space in immunocompetent individuals, sensitivity of the acid-fast smears is very low, rarely becoming positive (<10%). The acid-fast bacilli can be found in approximately 20% of HIV-positive individuals, and positivity is high in tuberculous empyema fluid due to a high number of bacilli [19, 20]. Pleural fluid cultures should be performed in any patient with an undiagnosed pleural effusion. *M. tuberculosis* is isolated by culture in only 20–40% of patients with proven TPE. The frequency of pleural fluid culture positivity is also high in HIV-positive patients. Combinations of pleural fluid and sputum cultures and repeated pleural cultures increase the detection rate of *M. tuberculosis* up to 80% [21, 22]. Both of the solid or liquid culture media might be used, but sensitivity is better with liquid culture media, and the duration of growth is shorter than that of solid media [23]. Although nucleic amplification assays are faster than conventional methods and enable direct detection of *M. tuberculosis* in clinical sam-

ples, they are not sensitive enough even Xpert MTB/RIF and not approved for routine use in pleural tuberculosis, and further studies are needed [24–27].

Histologic examination (epithelioid cell, caseating and noncaseating granulomas), acid-fast staining, and culture of the pleural specimens obtained by closed-needle biopsy can confirm the diagnosis in approximately 65–75% of patients with tuberculous pleuritis [28]. Furthermore, it can identify the other diseases causing the pleural effusion such as malignancy and other infections. Image-guided biopsies and thoracoscopic biopsies have high diagnostic rates compared to blind biopsies [29, 30].

The tuberculin skin test is negative in approximately 30–40% of cases and always negative in immunosuppressed patients. Negative results do not rule out the diagnosis; positive results may have only a supportive role in low endemic areas. Similarly, interferon-γ release assays are not helpful to distinguish active disease from latent infection. Both of the tests are not recommended for diagnosis of pleural tuberculosis [31, 32].

Current diagnostic tests are difficult and time-consuming and remain suboptimal. Besides these, quality of samples, methodology, and patient-related factors all are affecting the results.

For these reasons, a number of pleural fluid biomarkers such as adenosine deaminase (ADA), interferon-γ, interferon-γ-induced protein of 10 kDa (IP-10) and interleukin-27, pleural fluid lysozyme concentrations, neopterin, leptin, and a lot of cytokines have been sought for the rapid and easy diagnosis of tuberculous pleural effusion. Adenosine deaminase (ADA) is an enzyme of the purine salvage pathway that catalyses the deamination of adenosine and 2′-deoxyadenosine. Increase in ADA activity is associated with the stimulation and the maturation state of the lymphocyte, due to the immune cellular response against *M. tuberculosis*. Adenosine deaminase levels in body fluids can be measured rapidly. Many studies have shown the high sensitivity (92%) and specificity (90%) of pleural ADA >40 U/L for the early diagnosis of TPE in the predominance of lymphocytes. Even when acid-fast smears, cultures are negative and even in HIV-positive patients with very low $CD4^+$ T cells [33, 34]. The low levels of ADA almost rule out tuberculosis in low endemic regions [35]. Because pleural fluid ADA levels might be elevated in other conditions such as mesothelioma, cancer, bacterial empyema rheumatoid arthritis, and lymphomas parapneumonic effusions and conversely might be decreased with advanced age, results of ADA levels should be interpreted in parallel with clinical and other laboratory findings [36, 37, 38]. Interferon-γ is a pro-inflammatory cytokine released by activated CD4+ T cells, cytotoxic T cells, and natural killer cells which increases the mycobactericidal activity of macrophages. Elevated levels of interferon-γ were detected in tuberculous pleural effusions, and high sensitivity and specificity similar to ADA have been reported but the lack of optimized cut-off value limits its use [39, 40]. Interleukin-27 (IL-27) is a cytokine secreted by antigen-presenting cells and mediates interferon-γ production and T-helper type 1 response. It is suggested that measurement of pleural levels of IL-27 may aid the diagnosis of pleural tuberculosis especially with the combination of ADA values [41, 42]. However, pleural levels of biomarkers may contribute to the diagnosis of pleural tuberculosis when used in combination with other biomarkers and

clinical findings, but none of the biomarkers have adequate diagnostic potential by itself. Further studies are needed to validate them [43, 44].

2.6 Differential Diagnosis

A lot of diseases and conditions may cause pleural effusion such as malignancies (lung, breast cancer), congestive heart failure, pneumonia (bacterial, viral, fungal), abscesses (hepatic, subphrenic, splenic), inflammatory diseases (systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Wegener's granulomatosis), pulmonary embolism, lymphatic abnormalities, and ascites [2]. In the absence of presumptive clinical findings, the pleural fluid analysis may contribute to the diagnosis [45]. Despite the analyses of pleural fluid including cytology, exudative pleural effusion may remain unidentified in about one-fourth of patients, and pleural biopsies may be required. Fungal infections, vasculitis, autoimmune diseases, and sarcoidosis must be considered in differential diagnosis of the granulomatous pleuritis [46].

2.7 Management

Although the most of tuberculous pleural effusions resolve spontaneously, there is a high risk for recurrence, in nearly two-thirds of untreated patients for development of active pulmonary or extra-pulmonary tuberculosis within 2–5 years. The symptoms may be prolonged in untreated patients, and complications may develop. Considering these, all the patients with tuberculous pleural effusion should be treated. It should be tried to obtain specimens for culture and drug-susceptibility testing before the beginning of therapy. Drug-susceptibility testing should be performed for at least isoniazid and rifampicin.

Patients with sputum positivity for *M. tuberculosis* should be isolated. All patients with tuberculous pleural effusion should be tested for HIV infection.

In daily practice, if the definitive diagnosis could not be established, presumptive anti-tuberculosis therapy can be started to the patients with compatible clinical findings along with lymphocyte predominance exudative pleural effusion, consistent pleural fluid biochemistries, and exclusion of potential other causes or demonstrating granuloma on pleural biopsy [1]. Treatment of the TPE is the same as the standard active pulmonary tuberculosis. In addition to standard anti-tuberculosis chemotherapy and pleural drainage, the use of corticosteroids may be beneficial in selected patients.

Anti-tuberculosis therapy: Patients should be treated with isoniazid, rifampin, ethambutol, and pyrazinamide with pyridoxine for 2 months followed by 4 months of isoniazid and rifampin as in pulmonary tuberculosis [47, 48, 49]. Directly observed therapy and the daily dosing is recommended, and the use of thrice-weekly

dosing is not recommended throughout the course of therapy [47]. If drug-susceptibility test results are available initially and pleural tuberculosis is caused by multidrug-resistant *M. tuberculosis*, appropriate treatment regimen should be chosen according to the drug-susceptibility results. If the drug-susceptibility test results become available later, the empiric treatment regimen should be started and then adjusted according to the test results. With appropriate treatment, the symptoms subside within 2 weeks, pleural fluid is resorbed within 6 weeks, but the persistence of the fever and pleural fluid may be extended in some patients up to 2 and 4 months, respectively. Patients with HIV positivity or living in HIV-prevalent settings should receive at least 6 months of rifampicin-containing treatment regimen as patients without HIV infection. Potential drug-drug interactions must be considered.

Immune reconstitution inflammatory syndrome (IRIS) may develop in HIV-infected patients within the first months following initiation of antiretroviral therapy. Tuberculosis IRIS may also develop in HIV-uninfected patients particularly in with pleural and lymph node involvement up to 3 months of therapy. All the patients must be followed up closely [50].

Corticosteroids: Adjunctive use of corticosteroids may shorten the duration of the symptoms and pleural effusion. The patients with severe systemic syndromes may benefit from a short course use of corticosteroids. Corticosteroids may also reduce pleural thickening and pleural adhesions after the disease but the impact of them on long-term lung function is unclear [51]. There are some concerns regarding the use of corticosteroids in HIV-infected patients because of the possibility of increased risk of opportunistic infections and Kaposi sarcoma [52].

Pleural drainage: Routine drainage of pleural fluid is not recommended. If the patient has large pleural effusion causing dyspnoea, a therapeutically thoracentesis should be considered to relieve symptoms, and patients with tuberculous empyema may require decortication [53].

Complications: Pleural thickening, fibrosis, chronic chest pain, impairment in lung function, and dyspnoea are among the complications of tuberculous pleural effusions. Residual pleural thickening prevalence at the end of anti-tuberculosis treatment is varying between 5% and 55%, and most of them decrease with time. Although there are some data about the benefits of fibrinolytics on reducing the residual pleural thickening, data are insufficient and require further study.

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Chapter 3
Gastrointestinal and Peritoneal Tuberculosis

Sophia De Saram and Jon S. Friedland

3.1 Epidemiology

Autopsies of patients with pulmonary tuberculosis presenting in the pre-antibiotic era revealed intestinal involvement in up to 90% of cases [30]. In the current era, obtaining accurate data on gastrointestinal tuberculosis (GI TB) is limited by several factors. In many resource-poor settings, the diagnosis, treatment and reporting of infectious pulmonary disease take priority over that of extra-pulmonary disease. In some settings, limited access to diagnostics precludes the confirmation of GI TB. In many settings, the accuracy of reporting systems is variable. Cohort studies, whilst useful for gathering detailed information, are often subject to selection bias. For example, cohorts reported by surgical centres are likely to over-report the proportion of patients with GI TB requiring surgery.

With those limitations in mind, the available data shows that the epidemiology of gastrointestinal tuberculosis (GI TB) varies widely across the world. In Europe and the United States, it is the sixth most common site of extra-pulmonary tuberculosis (EPTB) [65, 74], whilst in Saudi Arabia GI TB was the most common site of EPTB [1]. In England, abdominal tuberculosis was found to be three times more common in patients from the Indian sub-continent than in patients of white ethnicity [71]. GI TB is predominantly reported as a disease of young adults with a mean age in the late third to early fourth decade [8, 36]. In Nigeria 10% of diagnoses of abdominal tuberculosis are in children [36], whilst in Europe children account for only 3.7% of the diagnoses [74]. The gender profile varies, with India and Pakistan [10, 18]

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describing a female predominance, whilst Saudi Arabia and the UK have an equal gender distribution [1, 8].

Whilst the majority of culture confirmed GI TB cases are caused by *Mycobacterium tuberculosis* [55], zoonotic tuberculosis caused by *M. bovis* still causes a significant proportion of disease in certain settings and it is likely that the impact of *M. bovis* worldwide is under-reported. The proportion of tuberculosis (of all anatomical sites) caused by *M. bovis* shows wide geographical variation, causing 2.8% of cases in Africa, 0.3% of cases in the Americas and 0.4% of cases in Europe with very little data from Asia and Western Pacific [59]. Within a cohort in California, USA, *M. bovis* accounted for 8% of the diagnoses of TB in adults and half of the diagnoses of TB in children [72]. In the Californian cohort, 97% of these diagnoses were in patients of Hispanic ethnicity. In contrast, three quarters of a UK cohort with *M. bovis* infection were born in the UK, and a similar proportion had been born before widespread pasteurisation of milk was introduced in the UK [53]. The variation in epidemiology of *M. bovis* is likely due to variations in the level of control of bovine tuberculosis in cattle, patterns of consumption of unpasteurized dairy products and migration.

Particular groups of people are at increased risk of GI TB. People with HIV infection are at higher risk of all forms of extra-pulmonary tuberculosis, and in some coinfected cohorts, GI TB has been reported as the most common extra-pulmonary site [37]. Within a resource-rich setting, HIV co-infection is associated with an increased incidence of *M. bovis* infection with a relative risk of 2.6–8.3 times that of HIV-negative patients [59]. This association has not been replicated in resource-poor settings.

Patients undergoing treatment with antitumour necrosis factor alpha therapy are at increased risk of tuberculosis infection. The proportion of extra-pulmonary disease, including GI TB, is higher than in the population overall [41]. Tuberculous peritonitis has been described, albeit rarely, in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Sixty-nine percent of the cases reported had no extra-peritoneal disease and no identified risk factor for TB [82]. In vitro studies suggest that changes in pH and osmolality may impair the function of white cells in the peritoneal fluid [42], and ongoing research in our laboratory shows that acidosis modulates many TB-specific immune responses. CAPD may thus increase the risk of TB peritonitis.

In resource-rich settings, alcoholic liver disease (ALD) has been linked with increased risk of peritoneal TB. In one study 62% of patients with peritoneal TB had ALD [76]. This strength of association is not seen in cohorts within resource-poor settings. The reason for this link is not entirely understood but may be related to the malnutrition and subsequent T-cell impairment associated with ALD.

3.2 Pathogenesis

The principle causative agent of GI TB, *Mycobacterium tuberculosis*, may infect the GI tract via the following routes: ingestion of bacilli in sputum from a focus in the lung, lymphatic or haematogenous spread from an active tubercular focus elsewhere in the body, direct spread from adjacent organs or ingestion of contaminated dairy products.

GI TB caused by *M. bovis* is transmitted primarily by ingestion of unpasteurised milk and milk products but can also be transmitted by inhalation of airborne particles from animal to human and, rarely, from human to human.

When mycobacteria bacilli are ingested either in sputum or in contaminated food products, their entry into the intestinal mucosa is aided by M cells which phagocytose the bacilli. M cells present the bacilli to dendritic cells and macrophages present in the parafollicular area of the mucosa-associated lymphoid tissue. Mycobacteria within tissue macrophages and monocyte-derived immature macrophages are able to escape killing and undergo cycles of intracellular replication and release into the extracellular space. Some infected macrophages may disseminate via the lymphatic or haematogenous routes. Interaction between T lymphocytes and mature macrophages leads to the formation of granuloma, supported by interferon γ and tumour necrosis factor α. A failure in the delicate balance that maintains these granuloma leads to liquefaction of the granuloma, tissue damage aided by matrix metalloproteinases and release of mycobacteria [24, 32, 49, 70]. A detailed review of the immunopathology of TB is beyond the scope of this chapter, but GI-specific factors have not been investigated or defined in any detail.

The tendency for GI TB to localise to the ileocaecal region of the intestine is thought to be due to the abundance of lymphoid tissue and the relatively longer contact time between intestinal contents and the mucosa in this section of the gut. The higher density of gut-associated lymphoid tissue in young adults may also partly explain the higher incidence of GI TB in this age group [23].

3.3 Clinical Presentation

The reputation of tuberculosis as a great mimic of other conditions is particularly true for GI TB. The clinical presentation of GI TB may be very non-specific and varies depending on the specific site of disease and the immune status of the host. It can present in a similar way to inflammatory bowel disease, GI infections such as amoebiasis, enteric fever and *Yersinia enterocolitica* and malignancy of the GI tract or other abdominal and pelvic organs. Only 15–25% of patients with GI TB have concomitant active pulmonary TB [35, 55]. These factors often contribute to a delay in diagnosis of GI TB with an associated increase in morbidity and mortality. Diagnosis of GI TB requires a high index of suspicion.

3.3.1 Intestinal TB

Whilst the majority of patients with intestinal tuberculosis present with insidious symptoms, with a mean symptom duration of 5–8 months, around a third of patients have been reported to present acutely with a surgical abdomen [1, 45, 64]. The most common symptoms in patients with intestinal tuberculosis are abdominal pain

(40–100%), weight loss (30–80%), fever (30–60%), nausea and vomiting (15–50%) and change in bowel habit (up to 50%) [1, 27, 29, 45, 64, 71]. The exact site of disease within the intestine determines the predominant presenting features. At least half of patients with intestinal tuberculosis have lesions in multiple locations along the GI tract.

3.3.1.1 Oesophageal Tuberculosis

Oesophageal lesions account for only 0.2–1% of all GI TB [1, 29, 35, 71]. The presenting feature is most commonly dysphagia but can include associated anorexia, weight loss, retrosternal pain and, rarely, bleeding. The formation of tracheoesophageal and mediastinal-oesophageal fistulae associated with respiratory tract or mediastinal lymph node tuberculosis has been described [38, 66].

3.3.1.2 Gastric Tuberculosis

Up to 2% of intestinal TB lesions are in the stomach. Presenting symptoms include abdominal pain, nausea and vomiting and weight loss. The clinical and endoscopic features can mimic peptic ulcer disease or gastric malignancy. Gastric tuberculosis presenting as gastric outlet obstruction has also been described [19, 29].

3.3.1.3 Small Bowel Tuberculosis

One third to a half of patients with intestinal tuberculosis have involvement of the small bowel [1, 29]. Abdominal pain, nausea and vomiting, abdominal distension and fever are the most common presenting complaints. In cohorts with GI TB presenting as an acute surgical abdomen, small bowel strictures account for half of the presentations [10].

3.3.1.4 Ileocaecal Tuberculosis

The ileocaecal area is the most common site of intestinal tuberculosis, with up to 80% of patients with intestinal tuberculosis having involvement of this site [27, 44, 64, 71]. The most frequent presenting complaint is abdominal pain, which may be generalised or located in the right iliac fossa. Vomiting, weight loss and diarrhoea are also present in half of patients. In 25–50% of patients, an abdominal mass is palpable in the right lower quadrant [35] which can be mistaken for a malignant mass or an appendix abscess.

3.3.1.5 Colonic Tuberculosis

Lesions of the colon are found in about 10% patients with intestinal TB. The most common presenting features are weight loss, abdominal pain, fever, anorexia and change in bowel habit. Bloody diarrhoea is reported in a third of patients which may mimic dysenteric illness [29]. The appendix is affected in 2–3% [29, 45] and can present in a similar manner to acute appendicitis or an appendix abscess. An abdominal mass may be palpable in up to half of patients with colon or appendix involvement.

3.3.1.6 Anorectal Tuberculosis

Anorectal involvement is rare, occurring in only 1% of intestinal TB cases. It may present with a rectal mass or with an anorectal fistula [1, 29].

3.3.2 Differentiating Intestinal Tuberculosis from Crohn's Disease

Crohn's disease, particularly in more developed countries, is the most complex differential diagnosis of gastrointestinal tuberculosis as the clinical and endoscopic features can be very similar and both diseases have a predilection for the ileocaecal region. There is evidence that the incidence of Crohn's disease is increasing in some developing countries and, in one cohort, 43% of patients who were ultimately diagnosed with Crohn's disease had previously received antituberculosis therapy [17].

Clinical features that may aid in differentiating the two diseases are the presence of perianal disease which is more common in Crohn's disease and high fevers which, in absence of an abdominal abscess, are suggestive of GI TB. Enlarged, necrotic lymph nodes and presence of ascites or peritoneal thickening on computed tomography have been described in GI TB but not in Crohn's disease [13]. There are no endoscopic features that reliably differentiate between the two diseases but longitudinal ulcers, anorectal involvement and cobblestone appearance are more common in Crohn's disease whilst transverse ulcers and a patulous ileocaecal valve are suggestive of GI TB [28, 46]. The low yield of microbiological investigations, as discussed below, means histology is a key modality in differentiating the two diseases. The presence of confluent or necrotic granulomata on histological examination is highly suggestive of GI TB, with caseous necrosis being essentially diagnostic [2]. A recently published model displayed a sensitivity and specificity of over 90% for identifying GI TB in a small validation cohort [47]. This requires further validation in larger, multinational cohorts.

3.3.3 Peritoneal Tuberculosis

The predominant clinical features of peritoneal tuberculosis are ascites (73%), abdominal pain (65%) (which is usually non-localised), weight loss (61%), fever (59%) and abdominal tenderness (48%) [73]. A small proportion (5–10%) has dry or plastic tuberculous peritonitis with minimal ascites. Five percent present with small bowel obstruction secondary to adhesions [15]. The clinical imaging, ascitic fluid and laparoscopic features of peritoneal tuberculosis can be difficult to distinguish from peritoneal carcinomatosis.

3.3.4 Presentation in Patients with Human Immunodeficiency Virus Infection

The clinical manifestation of GI TB in patients with human immunodeficiency virus (HIV) co-infection differs in certain ways to that in patients who are HIV negative. In HIV-positive individuals, GI TB is three times more likely to be associated with disseminated tuberculosis. Constitutional symptoms of high-grade fever, night sweats and weight loss are significantly more common than in HIV-negative individuals. In patients with HIV infection, ascites is a less prominent feature, whilst abdominal lymphadenopathy and involvement of the spleen and liver are much more common [25]. HIV-associated TB may only become clinically apparent following treatment of retroviral disease and the development of an immune reconstitution inflammatory syndrome or IRIS.

3.3.5 Presentation in Children

In children, abdominal tuberculosis affects the peritoneum in 45%, lymph nodes in 35% and the intestine itself in 20%. In up to a quarter, lymph nodes are involved in addition to either peritoneum or intestine. Presentation is usually with anorexia and weight loss (up to 70%) and abdominal distension (50%). Up to half of children with GI TB present to the surgical team with up to 10% of children having clinical peritonism detected at presentation. In contrast to the adult cohort, some paediatric cohorts have described concomitant chest abnormalities in as many as 50–75% of children, with up to 40% of children presenting with features of extra-gastrointestinal symptoms [22, 57, 83].

3.4 Investigation

A microbiologically confirmed diagnosis of GI TB occurs in anywhere between 10% and 70% of cases, depending on the exact site of disease and the availability of sampling and diagnostic modalities. Characteristic histology is the primary means of diagnosis in 30–40% of cases. The remaining diagnoses are made on the basis of a combination of clinical, epidemiological, radiological and histological features as well as a response to antituberculosis therapy. Culture or histology of samples from abdominal lymph nodes or from a distant anatomical site can also provide supporting evidence [1, 29, 44, 45, 67, 71].

3.4.1 Blood Parameters

Routine blood parameters of patients with GI TB reveal non-specific abnormalities with anaemia in 60%, erythrocyte sedimentation rate greater than 30 mm/hour in 67% and a raised white cell count in 28% [1, 27, 29, 45].

3.4.2 Radiology

3.4.2.1 Plain X-Ray and Barium Studies

Chest x-ray is abnormal in up to 25–45% of patients, and, whilst the changes are non-specific in the majority of cases, this may increase the index of suspicion for tuberculosis [1, 7, 71, 78]. In patients presenting with an acute abdomen, an erect chest x-ray is useful to look for free peritoneal air. Plain abdominal x-ray may reveal calcified lymph nodes and, in patients with strictures or bowel obstruction, dilated bowel loops.

Barium studies reveal abnormalities in 50–80% of patients with intestinal TB. These abnormalities include ulceration, strictures, deformities of the caecum and ileocaecal valve and accelerated transit [18, 27, 35, 44, 52, 57, 71].

3.4.2.2 Ultrasound

Ultrasound (US) is useful for detecting ascites, particularly in peritoneal TB with small volume ascites that is not clinically detectable. Ascites is also present in a third of intestinal TB cases and its detection helps to distinguish intestinal TB from Crohn's disease as ascites is rarely present in the latter [2]. The presence of septation, fibrinous strands or debris within the ascites, whilst not pathognomonic, raises the likelihood of TB. US reveals lymphadenopathy in 25–60% of cases and may

also enable visualisation of thickened mesentery or bowel wall [43, 44, 57, 73]. One major limitation of US is that images of bowel and the associated mesentery or lymph nodes can be obscured by overlying gas-filled loops of bowel.

3.4.2.3 Computed Tomography

Compared to ultrasound, computed tomography (CT) can further characterise peritoneal and lymph node changes, as well as imaging the whole intestine. CT of the abdomen with intravenous contrast reveals enlarged, peripherally enhancing lymph nodes with central low density, representing caseous necrosis, in 40–70% of patients with GI TB. Other lymph node patterns associated with GI TB include lymph node masses of mixed density, multiple mildly enlarged lymph nodes associated with bowel loops or mesentery and calcified lymph nodes. Whilst neither necrosis nor calcification of lymph nodes is specific to TB, they are highly suggestive [81]. The appearance of tuberculous peritoneal thickening on CT is usually smooth with marked enhancement, contrasting with the nodular, irregular thickening of carcinomatosis [33]. Other abnormalities that may be revealed on CT are bowel wall thickening, strictures, fistulae, inflammatory masses and adhesions (Fig. 3.1).

3.4.2.4 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is not widely available in many of the settings with the highest rates of GI TB. Even when it is available, it is a more time-consuming and costly investigation and therefore it is often used only in specific circumstances. For example, MRI may be used to avoid the radiation exposure of repeated CT scans in young patients. In circumstances where intravenous contrast is not available or is contraindicated with CT, plain MRI may yield more information than plain CT. Most findings on MRI, as on CT, are not specific to GI TB, but

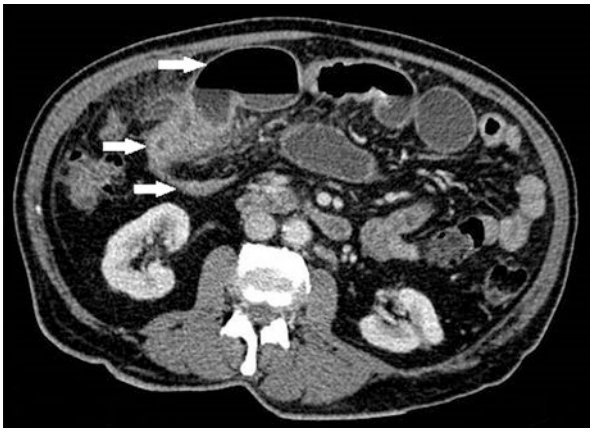

Fig. 3.1 Axial contrast-enhanced CT image showing thickened, stenosed area of small bowel (middle arrow) with surrounding mesenteric stranding. Dilated small bowel is seen proximally (top arrow) with collapsed small bowel distally (bottom arrow). *(With thanks to Dr Alison Graham, Imperial College Healthcare NHS Trust, London, UK for image)*

multilocular and peripherally enhancing abdominal lymph nodes are suggestive of TB. MRI is less sensitive than CT for detecting calcification within lymph nodes [39, 77].

3.4.2.5 Functional Imaging

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) uses the uptake of radiolabelled glucose to assess metabolic activity. A study examining its use in identifying the cause of peritoneal thickening found that the modality cannot reliably distinguish between malignant and tuberculous peritoneal thickening as both disease processes are associated with increased glucose uptake into the tissues [14]. To our knowledge there have been no studies specifically looking at the use of function imaging in intestinal TB although there are a number of case reports indicating that it may have a role. As the most common differential diagnoses, namely, inflammatory bowel disease and malignancy, are both likely to cause increased glucose uptake, it seems unlikely that functional imaging will eliminate the need for tissue sampling.

3.4.3 Methods of Tissue Sampling

3.4.3.1 Percutaneous Sampling

Ascitic fluid, if present, is the most easily accessible sample. However, as discussed below, the culture yield is poor. Blind peritoneal biopsy has been used for several decades, and the resulting samples allow histological confirmation of the diagnosis of peritoneal TB in 40–60% of patients. Documented complications from the procedure include bowel perforation and bleeding (1–2%) with associated mortality [11, 75, 80]. The yield of radiologically guided sampling of peritoneum or abdominal lymph nodes has been reported as around 50% in both adult and paediatric cohorts [44, 52]. Where resources allow, peritoneal biopsy under direct visualisation provides a higher yield, as discussed below.

3.4.3.2 Endoscopy

The macroscopic features of intestinal tuberculosis at endoscopy include ulcers, strictures, nodules, pseudo-polyps and distortion of the ileocaecal valve. When multiple ulcers are present, they can be interspersed with variable lengths of normal mucosa, as seen in Crohn's disease [84]. For more on distinguishing intestinal tuberculosis from Crohn's disease, see Sect. 3.3.2.

Endoscopic biopsy of lesions yields supportive histological information in 75% of cases [27, 44]. When mucosal abnormalities are beyond the reach of conventional endoscopes, push endoscopy or retrograde ileoscopy can be useful. Video capsule endoscopy may have a role in identifying a target for subsequent biopsy by these techniques or, on its own, for documenting extent of disease in the small bowel [61, 68]. Endoscopic ultrasound can be used for evaluation and sampling of mediastinal lymph nodes associated with oesophageal lesions [50, 69].

3.4.3.3 Diagnostic Surgical Procedures

The diagnostic yield from histology is increased when samples are collected by surgery with direct vision of the pathology. Laparoscopy is widely used for the investigation of ascites or peritoneal thickening of unknown cause. In cases of peritoneal TB, the most common macroscopic findings at time of surgery are ascites, yellow or white nodules on the peritoneum and peritoneal or visceral adhesions. The visual appearances alone have been reported to have a sensitivity of 84–100% and a specificity of 96–100%. The sensitivity and specificity of histological examination of samples gained from surgical biopsy are 70–100% and approaching 100%, respectively. The complication rate of laparoscopy as reported in older case series is 1.5–3% [16, 73] but this is almost certainly reduced now particularly when done by experienced operators.

In centres where laparoscopy is not available or in cases with extensive peritoneal adhesions, laparotomy may be used to gain tissue samples. In some older patient cohorts, 50% of laparotomies were performed purely for diagnostic purposes [57]. Open peritoneal biopsy under local anaesthesia is an alternative that has been used by some centres [79].

The role of diagnostic laparoscopy or laparotomy in intestinal TB is limited. In cases where the intestinal lesion is not accessible by available endoscopic methods, surgical approaches allow sampling of associated mesenteric lymph nodes [2].

3.4.4 Ascitic Fluid Analysis

Ascitic fluid samples from patients with tuberculous peritonitis usually contain 500–1500 white cells/mm^3, predominantly lymphocytes. However, a low white cell count does not rule out peritoneal TB, and a predominance of neutrophils, particularly in patients with renal failure, can also be found. The importance of neutrophils in the immunopathology has been overlooked until relatively recently [63]. A serum-ascites albumin gradient of <11 g/L is found in almost all patients with peritoneal TB without liver cirrhosis. However, the sensitivity is lower in patients with concomitant portal hypertension-induced ascites, and the specificity is low. An ascitic adenosine deaminase level of ≥30 U/L has a sensitivity and specificity of over 90%. The levels of LDH, CA-125 or glucose in ascites are not sufficiently discriminatory to be recommended routinely [73].

3.4.5 Histology and Cytology

Characteristic histology in the absence of positive microbiology contributes to the diagnosis of intestinal TB in up to 75% of cases [44, 71].

3.4.5.1 Intestinal Tuberculosis

Confluent granulomata and caseating granulomata in mucosal samples are considered diagnostic of intestinal tuberculosis but are only present in 25–50% of samples. Non-caseating granulomata are present in 60–70% of samples, and chronic inflammation and ulceration are common findings but are not specific to intestinal tuberculosis [2, 28, 44].

In up to 5% of cases of intestinal tuberculosis, histology of the intestinal tissue shows non-specific abnormalities, whilst the granulomata are present only in the associated mesenteric lymph nodes. Multiple lymph nodes may need to be examined in order to identify the granulomata.

3.4.5.2 Peritoneal Tuberculosis

When samples are taken under direct visualisation, non-caseating granulomata are found in 70–90% and caseating granulomata in anywhere between 33% and 100% of samples. Ziehl-Neelsen stain reveals acid-fast bacilli in 25–75% of samples and may be positive even when the macroscopic appearance of the peritoneum shows only mild erythema [34, 54, 60, 76].

3.4.6 Microbiology

3.4.6.1 Culture

In patients with peritoneal TB, Ziehl-Neelsen stain of ascitic fluid is positive in only 3–6%, and culture is positive in 16–35% [60, 73]. The culture yield increases to 66–83% if a large volume of ascitic fluid is centrifuged and the cell pellet cultured. Peritoneal tissue gives a higher yield with 50% being positive on stain and over 70% being culture positive. Intestinal tissue samples are culture positive in 25–35% [2, 4, 34, 52]. Auramine staining is also more sensitive.

The use of liquid culture media reduces time to detection of mycobacteria from 4 to 8 weeks with conventional solid media to a mean of 14 days. A further benefit of using liquid media is that it may better support the growth of *M. bovis* compared to standard Lowenstein-Jensen medium [31]. Cheap rapid tests such as the microscopic observation drug susceptibility (MODS) assay [58] may be effective in upper GI TB [48].

3.4.6.2 Nucleic Acid Amplification Techniques

TB polymerase chain reaction (PCR) provides a rapid diagnostic method but is limited by the requirement for the necessary equipment and laboratory personnel. Several studies report that PCR, targeting a region of the IS 6100 gene, has a sensitivity of 60–65% for intestinal tissue samples, but only 7% for ascitic fluid samples. The specificity of PCR is 100% [4, 28, 34].

The GeneXpert MTB RIF assay is an automated nucleic acid amplification test which requires minimal operator time and expertise and can produce a result in as little as 2 h. A meta-analysis found the sensitivity and specificity to be 81.2% and over 98%, respectively, for extra-pulmonary samples when compared to a composite reference standard. However, the sensitivity of GeneXpert when testing fluid samples (most data is from pleural fluid and cerebrospinal fluid) is lower and, when compared to a composite reference standard, is similar to conventional culture [21]. There is a lack of good data on the performance of GeneXpert MTB RIF specifically for intestinal and peritoneal samples.

3.4.7 Immunology

Tuberculin skin tests are positive in only 50% of patients with a diagnosis of GI TB, with higher positive rates of 80–90% described in some paediatric cohorts [20, 57, 73, 83]. Positive tuberculin skin tests are not specific to active tuberculosis and may represent latent infection.

A meta-analysis of the use of interferon-gamma release assays (IGRA) in the diagnosis of intestinal tuberculosis reported a positive and negative likelihood ratio of 6.02 and 0.19, respectively [62]. Given the inability of IGRA to distinguish between active and latent tuberculosis infection, international guidelines advise against their use in the diagnosis of active tuberculosis [86].

3.5 Management

3.5.1 Medical Management

For patients without HIV co-infection who have not undergone treatment for tuberculosis previously, treatment with standard quadruple antituberculosis therapy for 6 months has been shown to be as effective as longer courses [51]. In patients with proven or likely (due to local epidemiology, previous treatment or treatment failure) drug-resistant tuberculosis, treatment with a combination of antituberculosis antibiotics according to local or World Health Organization guidelines is appropriate. The place of newer anti-mycobacterial drugs such as bedaquiline and delamanid is not

clearly established in the management of drug-resistant gastrointestinal tuberculosis, but they are likely to have a role. In general, the approach to treatment of gastrointestinal and peritoneal tuberculosis is very similar to pulmonary disease except that the patient is not usually an infection risk to others.

The role of routine use of steroids in the management of GI TB has not been addressed by a randomised, controlled trial, and data from available publications are conflicting [3, 56]. However, it is unlikely that steroids will confer a treatment benefit in gastrointestinal disease and we do not recommend their routine use.

3.5.2 Surgical Management

The role of surgery in the management of GI TB has changed dramatically over the last 50 years with the introduction of effective antituberculosis therapy. Therapeutic surgical procedures are now reserved primarily for patients with acute surgical emergencies or as an adjunct in patients who are not responding to medical therapy alone. In recent adult cohorts, 15–32% of patients required surgery [27, 44]. In older paediatric cohorts, 7–20% of patients required surgical intervention, such as bowel resection or stricturoplasty for obstruction refractory to medical therapy [57, 83]. In a cohort of patients with intestinal TB and evidence of intestinal stricture on barium study, conservative treatment with antituberculosis therapy was successful in 91% with only 9% requiring surgery [5]. If possible, a conservative approach to management with fluid rehydration and nasogastric suction is to be preferred providing this can safely be maintained for sufficiently long for medical treatment to be effective.

3.6 Prognosis

Up to three quarters of patients with GI TB respond to medical therapy alone [44]. However, 10–15% of patients will develop partial bowel obstruction, 5–10% will develop complete bowel obstruction, 4–7% will suffer bowel perforation, 2–3% will have GI bleeding that requires intervention and 1–2% will develop fistulae [18, 27, 44, 71]. Protein losing enteropathy in 3% and chylous ascites in 2% have also been described as complications in a paediatric cohort [57].

The reported overall mortality from GI TB varies widely with some of the variation explained by inconsistent inclusion of patients who have been diagnosed at post-mortem. In paediatric patients the mortality rate is reported as 3–8%, being highest among those who present with intestinal perforation [52, 57]. In adults the reported mortality rate ranges from 5% to 50%, with older age, coexisting liver cirrhosis and delay of treatment being associated with a higher likelihood of death [12, 15, 16, 25, 44, 51]. However, the data comes from diverse

studies reported from different parts of the world at different times often when awareness of gastrointestinal tuberculosis was less well appreciated and definitive data is lacking. All data has to be interpreted with great caution, and it is likely that failure to consider the diagnosis is one of the greatest drivers of mortality.

3.7 Priorities for Research

The most pressing needs are for better diagnostic tests for gastrointestinal and peritoneal tuberculosis, better treatments for drug-resistant disease and biomarkers which predict early those patients at risk of a poor outcome. A study in India did show some promise with the use of PCR on faecal samples for the rapid, noninvasive diagnosis of intestinal TB [61], but further work is needed to validate these findings [9] and no clear progress has been reported in this area in the last 10 years. To our knowledge the use of Xpert MTB RIF on faecal samples in patients with suspected intestinal TB has not yet been investigated. There is much interest in TB biomarkers in the context of pulmonary disease [85], and it will be useful to see if any biomarkers are specific for extra-pulmonary or GI tuberculosis. There is a small pipeline of new drugs for TB, and in the era of increasing drug resistance, there is an increasing interest in host-directed therapies [26]. In addition, despite recent setbacks [6, 40], there remains a high level of interest in vaccination to either prevent or manage tuberculosis, but it is very unlikely that there will be an effective new vaccine within the next 5 years.

3.8 Summary

Intestinal and peritoneal tuberculosis can present with non-specific symptoms or symptoms related to the part of the GI tract affected. Crohn's disease is an important differential diagnosis. Patients may present not just to physicians but to surgeons who do not normally manage tuberculosis so a multidisciplinary approach is required. There are many diagnostic approaches, but definitive diagnosis often requires invasive tissue sampling which may not be readily available in all settings or for all age groups. Standard short-course chemotherapy should be curative for most patients and surgery only required in a small number with acute complications such as obstruction. Data on the worldwide burden of disease is lacking, and it is likely to be under-reported as the focus is on patients capable of spreading infection. Physicians must have a high index of clinical suspicion in order to make a timely diagnosis and institute best therapy. Biomarkers for this condition are urgently required.

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Chapter 4
Hepatobiliary and Splenic Tuberculosis

Cumhur Artuk and Hanefi Cem Gul

4.1 Hepatobiliary Tuberculosis

Involvement of the liver may develop due to the organ involvement primary infections caused by various infectious agents or as a component of a multisystem disease. Clinical symptoms usually mimic other clinical conditions. Tuberculosis is a disease of the developing countries, with rising indications in developed countries, especially in AIDS patients and in immigrant populations [1, 2]. Hepatic tuberculosis is a rare organ involvement of one of the most common infectious clinical conditions caused by *Mycobacterium tuberculosis*. Definition of hepatobiliary tuberculosis refers to the hepatobiliary involvement covering the isolated involvement of the liver, bile ducts, or other organ systems. The clinical course of hepatic involvement of tuberculous is variable and is used to describe the involvement of the hepatobiliary system. Tuberculosis may present with the following clinical manifestations including tuberculous pseudotumors, tuberculous cholangitis, tuberculous liver abscesses, and tuberculous hepatitis [3–7].

4.1.1 Epidemiological Features

Tuberculosis is a common disease with significant mortality and morbidity rates, especially in populations in underdeveloped or developing countries. Worldwide, it is estimated that two billion people have latent tuberculosis and seven to eight million new cases are detected each year. Despite the availability of effective treatments, two million people lose their lives due to this disease, especially in underdeveloped countries [8]. Although tuberculosis involves the lungs primarily,

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extrapulmonary involvements are seen at a rate of 15–20% and may involve any organ in the body [9]. Abdominal tuberculosis is not common but accounts for approximately 3.5% of extrapulmonary tuberculosis cases. Hepatic tuberculosis is very rare among other forms of abdominal tuberculosis. It is usually seen in cases with disseminated tuberculosis [8, 10, 11]. Primary hepatobiliary tuberculosis accounts for 1% of all tuberculosis cases [1, 12, 13]. In intra-abdominal tuberculosis, active pulmonary tuberculosis findings are present at the time of diagnosis in 6–38% of the patients [14].

Hepatic tuberculosis is more common in Asian countries, and hepatobiliary tuberculosis is common in Filipinos. A clear explanation of this fact has not been made available yet, but the observation supports that the Filipinos may have a racial predisposition to tuberculosis [1]. Localized hepatic tuberculosis has been reported in many case series in the worldwide literature, especially as an etiological factor of obstructive jaundice in Filipino patients [15–18]. Due to the lack of specific clinical findings and unavailability of specific diagnostic tests to help in diagnosing hepatic tuberculosis, the definite diagnosis is possible only after the histopathological examination of the resected tissues after surgery. In the autopsies, hepatic involvement is seen up to 90% of the pulmonary tuberculosis-associated deaths [11].

Hepatobiliary tuberculosis is twice as common in men than women. Although a specific age group has not been defined, one study reported that it was observed in the 11–50 age group more frequently [19].

4.1.2 Pathogenesis

Hepatic tuberculosis infection is a limitation to the disease by granuloma formation in the liver, independently of the routes of entry of the tuberculosis bacilli. Tuberculosis bacilli may reach the liver via hematogenous routes as it may be transmitted from the primary pulmonary infection site to the liver via the hepatic artery or from the gastrointestinal system via the portal vein. The transmission of the infection to the liver is possible via the lymphatic route, too, after the rupture of tuberculous lymph nodes [20, 21]. Hematogenous dissemination of the disease is more frequent than its dissemination via the lymphatic route or portal vein. In miliary tuberculosis, with intermittent attacks, hematogenous spread causes increased numbers of small tuberculosis foci in the liver.

In hepatic tuberculosis, granulomas can be either caseous or non-caseous. In miliary tuberculosis, central caseations and fibrinoid necrosis are observed in multiple small tuberculosis foci in the liver. In the periphery, coronas of variable diameter epithelial cells with embedded Langhans giant cells are present. These granulomatous tubercles are surrounded by a large number of lymphocytes. Tuberculous granulomas are most commonly found in the periportal area. In miliary tubercles or local tuberculosis, primary tuberculous complexes combine to form

tuberculomas. They form nodules of 1–4 cm in diameter. Embedded calcifications are the typical features of tuberculomas and they eventually become encapsulated. These nodules are sometimes the source of hematogenous spread.

Hepatobiliary tuberculosis is manifested in various clinical pictures depending on the characteristics of its pathogenesis [2, 9]:

1. *Incidental*. Liver involvement is seen in the autopsy of 25–50% of patients who die from active pulmonary tuberculosis.
2. *Miliary tuberculosis* (due to hematogenous spread of tuberculosis bacilli) causes multiple granulomas in the liver. This is the most prevalent and common form of hepatic tuberculosis, and it is reported that it is seen in 50–80% of all patients who died from pulmonary tuberculosis [11].
3. *Granulomatous hepatitis*. Tuberculomas coalesce reaching nodule sizes of 1–4 cm. Patients present with fever of unknown origin, jaundice, hepatomegaly, ALP elevation, and abnormalities in other liver function tests. Liver imaging may display normal findings, or nonspecific abnormalities may be observed. Laparoscopy is useful, revealing irregular nodules with white cheesy appearances on the surface of the liver. In the biopsy materials taken from these lesions, cheesy granulomas are observed. Granulomatous hepatitis with multiple granulomas in the liver may occur following BCG vaccination, especially in immune-compromised individuals.
4. *Nodular disease*. These lesions develop in the form of single or multifocal lesions in the liver and are seen as low-density, non-expanding lesions with or without peripheral extension. Observation of this type of structures necessitates the differential diagnosis from lymphomas, fungal infections, and metastases. The diagnosis should be confirmed by a fine needle aspiration biopsy with the imaging-guided techniques.
5. *Tuberculous liver abscess*. Tuberculous abscesses in the liver are very rare. Clinical and imaging features display similarities to pyogenic and amebic abscesses. The diagnosis is made by the cultivation of tuberculosis bacilli from the aspirated material.
6. *Tubular (ductal) disease*. These patients present with the clinical manifestations of obstructive jaundice due to the involvement of the bile ducts. Biliary involvement may develop due to the diffuse involvement of the intrahepatic bile ducts by tuberculosis bacilli or due to the pressure on the bile ducts caused by swollen tuberculous lymph nodes. ERCP demonstrates multiple intrahepatic biliary strictures and displays areas of ectasia and dilatation, helping to discriminate between cholangiocarcinoma and sclerosing cholangitis. Biliary strictures can take place in the hilar region or can be widespread in the distal bile ducts, characterized by dilatation of the intrahepatic bile ducts [2].

4.1.3 Clinical Features

The clinical findings of hepatobiliary tuberculosis are nonspecific similar to those of the extrahepatic disease, and hepatic involvement is usually asymptomatic. In various case series, nonspecific abdominal pain and right upper quadrant pain have been reported as the most common symptoms. The common symptoms and signs are as follows [3, 12, 19, 21]:

Right upper quadrant pain	65–87%
Nonspecific symptoms (fever, anorexia, weight loss)	%55–90
Nonspecific abdominal pain	50%
Jaundice	20–35%
Hepatomegaly	70–96%
Splenomegaly	25–55%

As it is usually the case with extrapulmonary tuberculosis, the patients usually present with a fever of unknown origin. Some other complaints such as anorexia and weight loss are included in the clinical picture. With the advancing disease, an initially nonspecific abdominal pain develops in the whole abdomen, and then it localized in the right upper quadrant [3, 22]. It occurs in approximately 55–90% of patients.

Clinical findings suggesting acute cholecystitis or biliary colic can be manifested in isolated biliary tuberculosis. The presence of jaundice suggests biliary involvement, and the biochemical test results may mimic extrahepatic biliary obstruction. Jaundice or biliary stenosis are recognized to be due to the following factors including portal hepatic lymph nodes pressing on to the bile ducts, pericholangitis, direct involvement of the biliary epithelium, and rupture of tuberculous granulomas located in the bile ducts [23]. Intrahepatic biliary obstruction may develop as a result of the granulomatous involvement, often as part of miliary tuberculosis. Tuberculosis of the bile ducts can develop with dilatations in the bile ducts accompanied by widespread strictures of the hepatic ducts. The patients with these pathologies present with painless jaundice and weight loss, often mimicking pancreatic carcinoma or cholangiocarcinoma. Only 45% of the jaundiced patients have accompanying abdominal pain [18].

The patients with tuberculous hepatic abscesses present with nonspecific symptoms; fever and abdominal pain being the major ones. Weight loss and jaundice are other findings [12, 18, 21, 24, 25]. Isolated pancreatic tuberculosis may occur with clinical manifestations similar to those of pancreatic neoplasms.

Hepatomegaly is the most common finding and observed in 70–96% of patients, mimicking isolated liver tumors or liver abscess [18, 21]. In approximately half of the cases mimicking liver cancers, the liver is hard and nodular; therefore, the clinical picture is the same as that of a neoplasm. There is a similar pattern in 36%

of the cases mimicking liver abscesses. Splenomegaly is seen in 25–55% of patients [3, 18].

4.1.4 Diagnosis

As the hepatobiliary diagnosis is challenging due to the variable symptomatology, there is a need for high-level evidence [26]. Biochemical tests indicating the presence of hepatic tuberculosis are not specific. Although the liver function tests, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, total protein, and albumin-globulin ratios, are high in 30–80% of patients, they are neither specific nor pathognomonic for the diagnosis of hepatobiliary tuberculosis [18]. A disproportionately high level of serum alkaline phosphatase is a supportive finding consistent with an infiltrative hepatic process. In hepatic tuberculosis, transaminases are detected at higher levels compared to ALP. However, in cases with biliary or portal vein involvement, ALP is higher. Compared to the obstruction-associated parenchymal disease, bilirubin levels are observed to be higher in extrahepatic tuberculosis. Alterations in the levels of bilirubin, INR, and albumin constitute the evidence of progression to liver failure [9]

While liver tuberculosis can be detected in advanced diagnostic processes in patients with pulmonary tuberculosis, approximately 75% of the patients have an abnormal chest radiograph that supports pulmonary tuberculosis [9, 25]. Imaging techniques play a key role in the diagnosis of hepatobiliary tuberculosis. The observation of calcifications on the liver lodge in the abdominal radiogram is sometimes seen in local hepatic tuberculosis. Ultrasonography (USG) does not only provide a diagnosis of hepatobiliary tuberculosis but also allows the detection of advanced clinical signs such as LAP, ascites, and fluid [27–30]. In ultrasonography, tuberculous liver abscesses and pseudotumoral liver tuberculosis are displayed as single or multiple complex masses and hypoechoic lesions with no significant walls, difficult to differentiate from carcinomas. Computed tomography (CT) and magnetic resonance imaging (MR) are helpful in the diagnosis of tuberculomas or tuberculous liver abscesses. Due to the caseous necrosis, liver tuberculomas are displayed as nongrowing central low-density lesions with a slightly formed peripheral rim, corresponding to the surrounding granulation tissue. However, these findings are also observed with the necrotic tumors, such as hepatocellular and metastatic carcinomas [31, 32]. The liver calcifications can also be demonstrated by a CT scan. The findings obtained by means of USG- and CT-guided aspiration and biopsy are important contributors to diagnosis [33]. Endoscopic USG (EUS) is a routinely used method in the follow-up of the pancreatic and biliary lesions, allowing sampling from these affected sites [34, 35]. These methods can also be used in liver lesions. USG- and CT-guided biopsies are the first choices because of the fact that EUS is more invasive and the availability of experienced personnel is limited [36]. MR does not provide an additional advantage in the diagnosis of hepatobiliary TB.

In hepatobiliary tuberculosis, the difficulties in making the diagnosis remain even after sampling of the related tissue. Microscopy, culture, histology, ELISA, and PCR are all important in making the diagnosis [37, 38]. However, the rate of diagnosis varies depending on the availability of the relevant sample and the availability of these tests. A definitive diagnosis of hepatic tuberculosis, either local or diffuse, is made by the histopathologic demonstration of caseous granulomas, by direct inspection of the ZN-stained biopsy specimen, or by the cultivation of the acid-fast bacilli. The aim should be to demonstrate the presence of tuberculosis bacilli in the liver directly or by cultivation. Granulomas are usually 1–2 mm in size, but large tuberculomas of up to 12 cm have also been reported. Epithelioid granuloma formation in hepatic TB may occur in 80–100% of cases. Brucellosis, coccidioidomycosis, and Hodgkin's disease should also be kept in mind in the differential diagnosis, because of the presence of granulomas in the courses of these diseases [39–41]. In 33−100% of liver biopsies taken from several cases, caseifications are observed as a characteristic finding of tuberculous granulomas [12, 25, 42, 43]. The rates of identifying the acid-fast bacilli in the biopsy and aspiration samples of the cases with hepatic tuberculosis range from 7% to 59% [12, 25, 44]. A positive tuberculosis culture confirms the diagnosis; however, the cultures provide positive results at a rate of 10% [42]. When the results and findings of the culture and microscopic examination are combined, the diagnosis rate rises to 30–50% [9].

T-SPOT or QuantiFERON tuberculosis tests detect the presence of interferon-γ, produced by the peripheric mononuclear cells in response to the specific antigens of *M. tuberculosis*. Recently, it has been used at high rates in the diagnosis of tuberculosis, and, with the sensitivity rates reaching up to 70–90%, it is more specific than the tuberculin skin test [45]. Among the molecular methods, PCR is pathognomonic in most of the patients with hepatic tuberculous granulomas. While the studies have determined 100% positivity in patients with confirmed diagnosis of tuberculosis (patients with caseous granulomas), the success rate was reported to be 78% in patients with a pre-diagnosis of hepatobiliary tuberculosis [46].

In cases with diagnostic failures despite the imaging techniques and laboratory tests, laparoscopy can be performed to diagnose the clinical forms of hepatic tuberculosis and to make a differential diagnosis. Laparoscopy allows inspection of the lesions and sampling of relevant material [3, 18]. In the diagnosis of bile duct tuberculosis, especially in cases with obstructive jaundice, ERCP applications provide valuable contributions to both the diagnosis and the treatment [42].

Sensitivities of the diagnostic methods [1]

Impaired liver function tests	30–80%
Abnormal pulmonary radiogram	75%
Histopathological evaluation	
Epithelioid granuloma formation	80–100%
Caseification	33–100%
Acid-fast bacilli	60%
PCR	88%

4.1.5 Treatment

Except for the differences in the treatment duration, hepatic tuberculosis treatment is the same with the other clinical forms of extrapulmonary tuberculosis. Conventional four-drug antituberculosis therapy is still the cornerstone of the treatment in alignment with WHO's recommendations [9]. The treatment consists of combination of four drugs: isoniazid (5 mg/kg/day), rifampicin (10 mg/kg/day), pyrazinamide (30 mg/kg/day), and ethambutol (20 mg/kg/day). In general, the four-drug therapy is initially administered for 2–4 months, followed by isoniazid and rifampicin treatment for 6–12 months. Although a 6-month duration is usually sufficient for the antituberculosis treatment, alternative regimens are needed due to multidrug-resistant bacilli or hepatotoxic drugs. Especially idiosyncratic secondary liver damage secondary to isoniazid may develop and can be fatal. A close follow-up of the patient can prevent this mortality. The American Thoracic Society recommends close monitoring of the serum ALT levels especially in patients who consume alcohol; in patients using other hepatotoxic medicines; in HIV-positive patients; in patients with abnormal baseline ALT levels; in patients with a previous history of a liver disease, viral hepatitis, and hepatitis associated with isoniazid; in pregnant patients; and in patients who are in the postpartum 3-month period [31]. With the standard antituberculous treatment, some studies have demonstrated relief of the abdominal pain and fever in 67% of the cases, increased appetite and weight gain, liver regaining its normal sizes, and significantly decreased mortality rates when the combination of rifampicin and INH combination is used [12].

Accompanied with the percutaneous drainage and aspiration of the abscess, the use of antituberculosis medication for at least 6 months in tuberculous liver abscesses increased the treatment success [5, 31, 38, 39, 47]. Due to the challenges in making the diagnosis, especially in cases of nodular hepatic tuberculosis, and because of the malignancy potential of the lesion, hepatectomy may be considered as an alternative treatment [48]. If no improvements are observed in the clinical course of the patients with obstructive jaundice despite the application of ERCP and stenting in addition to the antituberculous treatment, these patients may undergo percutaneous biliary drainage or surgical decompression.

The cumulative mortality rate in hepatic tuberculosis is 15–42%, and mortality due to hepatic failure is rare [12]. Respiratory failure and variceal bleedings developing secondary to cirrhosis are other causes [18]. The risk factors for poor prognosis are:

- Miliary tuberculosis
- Concomitant use of steroids
- Age younger than 20 years
- Cachexia
- HIV positivity
- Cirrhosis
- Hepatic failure

4.1.6 Complications

Penetrating the bile ducts, tuberculous nodules may cause tuberculous cholangitis, leading to strictures in the affected areas [23]. The presence of tuberculosis bacilli and caseous necrosis in these tuberculous nodules may cause hepatic cavity formation. Thus, the differential diagnosis of tuberculous abscesses, growing abscesses, or pseudotumoral liver tuberculosis becomes more difficult [18]. Development of portal hypertension with variceal bleeding as a consequence of the pressure caused by the tuberculous lymph nodes is a rare clinical manifestation of hepatobiliary tuberculosis. Tuberculous pseudocirrhosis may emerge due to scarification or diffuse dissemination of multiple tubercles in small amounts during the recovery process; however, it does not develop as a sequela of the recovery process of the major hepatic dysfunction. Hepatic amyloidosis and liver dysfunction may develop in chronic pulmonary tuberculosis [49]. Massive miliary spread to the liver may result in acute liver failure, as well as septic shock accompanied by multi-organ failure [50].

4.2 Splenic Tuberculosis

Splenic tuberculosis was described for the first time by Coley in 1846 as the secondary enlargement of the spleen due to tuberculosis either with limited involvement of other organs or without any other organ involvement [51]. Apart from a few case series, splenic tuberculosis is quite rare [52, 53]. Splenic tuberculosis develops mostly in immune-compromised patients usually following the hematogenous dissemination from an *M. tuberculosis*-laden focus. As a manifestation of miliary tuberculosis, it ranks the third after pulmonary and hepatic involvement [54–57]. An isolated splenic tuberculosis is quite rare especially in the immune-competent patients [57–60]. Extrapulmonary tuberculosis is still a public health concern in developing countries. The common forms of the extrapulmonary tuberculosis are tuberculous lymphadenitis, pleural tuberculosis, the involvement of bones and joints, abdominal tuberculosis, tuberculous pericarditis, tuberculous meningitis, and miliary tuberculosis [61–63].

4.2.1 Epidemiology

After the steady decrease in the 1970s, the incidence of tuberculosis has been observed to be on the rise in the developed countries as well following the AIDS outbreak in the 1980s [63, 64]. Although pulmonary tuberculosis is the most common form, the incidences of the disseminated and extrapulmonary tuberculosis have recently increased [65]. Clinical pictures of extrapulmonary disease with

osteoarticular, cerebral, and renal involvement are observed in 70% of the patients with tuberculosis and HIV infection [40]. 15–20% of all tuberculosis cases are extrapulmonary, and of them, 3–11% are abdominal [66, 67]. Abdominal tuberculosis is seen in the ileocecal junction, anorectal region, lymph nodes, and peritoneum. Venous thrombosis and splenic abscess cases have been reported in immune-compromised patients with tuberculosis. However, isolated splenic venous thrombosis and multiple splenic abscesses are quite rare in immune-competent patients [61]. In some case series, splenic tuberculosis is reported at a rate of 8%, and the rate of the micronodular involvement is reported to be around 5% [52]. Several postmortem studies report that the incidence of splenic tuberculosis is quite low (0.14–0.7%) and the cases are usually associated with septicemia [68].

According to the 2016 Global Tuberculosis Report of the WHO, tuberculosis remains to be one of the 10 most common causes of mortality and morbidity, even surpassing the mortality rates attributed to HIV infections. According to the report, in the year 2015, 10.4 million people were infected with tuberculosis worldwide, and 1.4 million deaths were attributed to this disease. According to the surveillance data of the WHO, tuberculosis is a major issue in Africa. In the same report, of all new cases in the world, 26% of them were reported to be seen in Africa with an annual incidence of 275/100000, which is half of the worldwide incidence of 142/100000 [69]. In HIV-1-infected patients with low CD4 counts, splenic or hepatic tuberculosis can be the initial clinical manifestation of tuberculosis. Diagnosis is difficult and often can be missed.

The risk factors involved in the development of splenic tuberculosis are listed below [70, 71]:

- Immune suppression (HIV positivity, SLE, steroid users)
- The presence and dissemination of pyogenic infections
- Splenic abnormalities
- Previous history of splenic trauma
- Sickle cell anemia
- Other hemoglobinopathies
- *M. tuberculosis* infection at another site in the body in immune-competent patients
- Presence of gastrosplenic fistula [72].

Immune-competent individuals without any valid risk factors prove the enigma of the diagnosis. Identifying a sequestered microbial agent in an isolated region like the spleen is challenging, and it is common to miss the diagnosis [73].

4.2.2 Clinical Features

In the literature, the characteristic initial clinical finding of the splenic tuberculosis is a fever of unknown origin [74, 75]. Besides the most common symptom of fever (82.3%), other symptoms are seen including fatigue and weight loss (44.12%),

splenomegaly (13.2–100%), spontaneous rupture of the spleen, hypersplenism, portal hypertension with or without gastrointestinal system bleeding, and fulminant forms with rapid progression [66, 76, 77]. Fever, cachexia, hemorrhage, and a rapid progression of sepsis are seen in the forms of the disease with a fulminant course [77]. Rarely, patients can be asymptomatic and can remain undiagnosed. Pain is not common [54]. Hematological abnormalities with decreased cell counts and polycythemia have been reported in case reports [78]. Ambiguous and nonspecific clinical symptoms and lack of characteristic radiological findings cause uncertainties in the diagnosis of isolated tuberculosis [55, 63, 70].

Case reports of splenic tuberculosis have been reported in the literature. One of them describes a patient presenting with the complaints of getting tired quickly, weakness, dyspnea, and night sweats. In the physical examination, splenomegaly was detected. Hypoechoic and hypodense lesions were reported in the ultrasound and in the computerized tomography (CT) examinations, respectively. In addition, intrathoracic and intra-abdominal lymphadenopathies (LAP), too, were identified in the CT. A chronic lymphoproliferative syndrome was considered; however, splenic tuberculosis was diagnosed in the histopathological examination, so to say, surprisingly [79].

Abscess formation is rare in splenic tuberculosis, and it is seen most commonly in HIV-positive patients [61]. Deep vein thrombosis, although very rare, should be considered especially in cases with widespread and severe tuberculosis [80]. Thrombotic events associated with tuberculosis can occur at various locations such as the hepatic vein or cerebral venous sinuses. As with other infectious diseases, tuberculosis can cause thrombosis by various mechanisms [61] including:

- Local invasion
- Venous compression
- Hypercoagulable state

Impaired fibrinolysis and increased plasma fibrinogen, as well as decreased levels of antithrombin III and reactive thrombocytosis, cause the development of DVT in tuberculosis [61].

A nontraumatic spontaneous splenic rupture is very rare; however, it is a life-threatening emergency. It ultimately ends up with death in 100% of the cases if remains undiagnosed and untreated. In the etiology of the spontaneous splenic rupture, malignancies rank the first with a rate of 30.3%, and infections rank the second with a rate of 27.3%. The concomitant presence of both of these etiologies is quite rare. In the literature, a case with spontaneous splenic rupture as a complication of concomitant splenic tuberculosis was reported in a patient with acute myeloid leukemia [81].

The findings including worsening of the patient's clinical condition, progressions in the existing lesions, or emergence of new lesions under treatment are defined as the paradoxical reaction. A paradoxical reaction is typically associated with increased inflammatory findings such as pulmonary involvement, lymphadenitis, and fever. Rapid destruction of bacilli with antibiotic treatment causes microbial components to be released in large quantities, leading to increases in the inflamma-

tory response. Persistent mycobacterial antigens cause hypersensitivity reactions. A paradoxical reaction can be clinically overlooked, causing termination of the treatment in tuberculosis patients due to misdiagnosis. Moreover, the paradoxical reaction limits itself; therefore steroid treatment is not required in all of the cases [70].

4.2.3 Diagnosis

PPD is usually positive in these patients. However, it is not reliable in endemic countries, in immunocompromised patients, and in BCG-vaccinated patients. PCR is more sensitive and specific, allowing identification of the subtypes of the organism. Abdominal ultrasonography (USG), which is noninvasive and cost-effective in these cases, can display miliary tuberculosis, nodular tuberculosis, tuberculous splenic abscesses, calcified tuberculous lesions, or a combination of them [73]. Tuberculomas can be described as the multiple hyperechoic lesions, which are well-demarcated by posterior expansion. When these lesions are displayed, the following diseases including lymphomas, acute leukemia, angiomas, metastases, and fungal infections should be considered in the differential diagnosis [57]. Abdominal CT is superior to the abdominal USG in determining the organ involvement, displaying multiple demarcated hypodense lesions which can be identified in clinical conditions other than splenic tuberculosis (8.21). CT can display a homogenous splenomegaly or tuberculomas as non-expanding homogeneous hypodensities [53, 77]. In cases with solitary massive splenomegaly, the following clinical conditions including cysts, hematoma, fungal infections, abscesses, infarction, lymphoma, and vascular or metastatic tumors should all be considered in the differential diagnosis [70]. Although no typical morphological appearances have been defined, thin and thick needle aspiration biopsies of the spleen are valuable, and the histopathological diagnosis is important (sensitivity 88%, specificity 100%) [54, 57, 67, 70, 77]. A microscopic examination defines the histologic type of the lesion as well as the stage of the tuberculous lesion, allowing the differential diagnosis of other granulomatous lesions and other confounding radiological lesions like lymphoma. Formalin tissue fixations and xylene processing lower the sensitivity of acid-fast staining (AFS), causing false-negative outcomes. The formalin-fixed and paraffin-embedded tissues cause failures in identifying tuberculosis bacilli on acid-fast microscopy. The real-time PCR examination of the sampled tissues of these cases has higher sensitivity superior to AFS. CNB (core needle biopsy) has a high diagnostic value in the diagnosis of splenic pathologies with a higher diagnostic accuracy for identifying the characteristics of the splenic lesion compared to the FNAC (fine needle aspiration cytology). A tuberculous infection is confirmed histologically by the presence of granulomas containing epithelioid and Langhans giant cells together with typical caseifications [70]. A reference culture test is used for the definite diagnosis currently [69]. In cases of fever of unknown origin with splenomegaly, tuberculosis should be kept in mind. Detecting caseified granulomas histopathologically will be pathognomonic. When the diagnosis cannot be made with noninvasive methods,

laparoscopy may be indicated. However, splenectomy should be considered as a last effort for the diagnosis. Drainage is required in splenic abscesses since the radiologic diagnostic methods are insufficient in these cases. The detection of acid-fast bacteria is possible rarely by microscopic examination; therefore, molecular methods still remain to be the valuable methods for a fast diagnosis of tuberculosis [63].

4.2.4 Treatment

Antituberculosis therapy is the first option in the treatment [53, 66, 76, 77]. Triple- or four-drug combination therapy should be maintained for a duration of at least 12 months. Except for some rare clinical conditions, splenectomy is an ineffective treatment method [61, 66, 77].

Indications for splenectomy [53, 55, 56, 61]:

- Antituberculosis treatment failure and presence of cytopenia or polycythemia
- Splenic tuberculosis with GIS bleeding secondary to portal hypertension
- Percutaneous abscess drainage failure
- Presence of multiple splenic abscesses
- Presence of splenic rupture

Antituberculosis treatment should be maintained until the postsplenectomy period. USG and CT imaging modalities can be utilized to evaluate the success of the treatment [78]. MRI and PET imaging are useful in determining the activity of the splenic lesion and in identifying other activities and fibrotic scars [82].

As the cases with splenic venous thrombosis are rare, controlled studies evaluating the efficacy of the anticoagulant treatment are unavailable. Anticoagulant treatment is not recommended in asymptomatic patients [83]. The potential benefit of the anticoagulant therapy is to prevent the thrombus formation in the portal, postportal, and portosystemic collateral veins. Tuberculosis should be considered in the differential diagnosis in cases with isolated visceral venous thromboses. Antituberculous therapy should be given as an adjunctive treatment, especially in cases with mesenteric involvement [61].

4.2.5 Complications

If the diagnosis of splenic tuberculosis is delayed and antituberculosis treatment is not initiated timely, intracranial tuberculosis abscesses and pulmonary tuberculosis may develop as complications after surgery. Systemic dissemination can be seen; however, starting antituberculous therapy will help in the recovery [71].

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Chapter 5
Lymphatic Tuberculosis

Yakup Hakan Basaran

5.1 Epidemiology

Formerly, since Hippocrates, the terms ‘scrofula’ or ‘king’s evil’ stood for all cervical lymph node swellings. Upon the discovery of tubercle bacillus in 1882, the causative agents for lymph node diseases became to be distinguished, and cases due to *Mycobacterium tuberculosis* are named as glandular tuberculosis. Moreover, it was determined that *Mycobacterium tuberculosis* was not the only causative agent for lymph node diseases.

Lymphadenitis due to tubercle bacilli was seen mostly among children and assumed to be a childhood manifestation of tuberculosis. Müller George P shared one of the earliest available statistical reports over tuberculous lymphadenitis (TL) and noted the peak incidence age group as 2–17 years old [21]. In time, until the 1970s, with the rise of the awareness of preventive measures, the overall incidence of tuberculosis decreased. William C Voorsanger stated in 1937 that the death rate from tuberculosis decreased from 325 per 1,000,000 to 58 and the main decline took place in the age group of 1–10 years in which TL was most common [42]. Though, especially since the 1970s, synchronously with the rapid spread of HIV infection, the average incidence interval for TL changed from childhood to 20–40 years [30]. The rise of the haematological malignancies and the use of immunosuppressant medications to prevent rejections in solid organ transplantations also contributed to the rise of tuberculosis and its complications within the adult age group. Ilgazli et al., in a study, consisted 636 cases with ages from 1 year to 89 years, found that the mean age for EPTB cases was 22.5 [17]. The result of another study performed by Mihai Raul POPESCU demonstrated a mean age of 35 years among 362 EPTB cases [32]. Muluye et al. from Northwest Ethiopia published the highest prevalence of TL within the age group of 15–24 and followed by the age group of 25–34 years [25].

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Mycobacterium tuberculosis complex is the main cause of TL and consisted of a group of microorganisms [15]. *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti* and *Mycobacterium canettii* are the bacteria in this group. Although the main target of mycobacteria is the lung, the bacilli may spread out from the lungs to other organ and tissues during the active phase or reactivation of the latent disease and form extrapulmonary tuberculosis (EPTB), and TL is the most common EPTB manifestation. Additionally, bovine tuberculosis agent *Mycobacterium bovis* and a variety of nontuberculous mycobacteria may infect especially cervical lymph nodes when contaminated dairy products consumed without pasteurisation.

Study	Period	No of cases	LN involvement %
Frossbohm et al. (2008) [48]	1996–2000	5675	39.8
Chan-Young et al. (2002) [49]	1996	1283	36.5
CDC [50]	2007	2697	42.5
Chandir et al. [8]	2005–2007	194	35.6
Rodriguez et. al. [33]	2003–2008	146	34.9
Popescu et al. [32]	1990–2012	732	49.45

In the surveillance report for tuberculosis in 2016, the US centre for disease control [6] indicates percentages of pulmonary, extrapulmonary and both pulmonary-extrapulmonary cases has been increased as 69.6 %, 20.3 % and 9.9 %, respectively, throughout the USA. The report also indicates the lymphatic tissue is the most common extrapulmonary destination for tuberculosis with a high percentage of 35.8% among in all extrapulmonary tissues affected by mycobacteria. Tuberculous lymphadenitis may infect all the lymphatic tissue, but the most common infected site is the cervical lymphatic region.

Not only the coexisting diseases but the burden of the infection across the geography has a great impact on the statistical data. In high-burden countries, extrapulmonary tuberculosis rates are reported to be higher. WHO Global tuberculosis report in 2017, demonstrates percentages of extrapulmonary tuberculosis rates as global and WHO regions Africa, The Americas, Eastern Mediterranean, Europe, Southeast Asia, Western Pacific as 15%, 16%, 15%, 24%, 15%, 15% and 8%, respectively. The European centre for disease control [12] 2013 report points out a percentage of 22.3% extrapulmonary tuberculosis cases across EU, while the US [6] report notes a percentage of 30.2% extrapulmonary tuberculosis cases across the USA. Another author Teresa Gomes et al. reported an overall 17% of EPTB in Brasil between the years 2007 and 2011 [14].

Gender and place of origin also play an important role in the development of TL. Although tuberculosis is more common in males, EPTL is more common in females. Statistical reports usually demonstrate female to male ratio as 1.4:1. In a study in Romania including a large number of cases, Mihai Raul Popescu reported a ratio of male/female TL cases as 0.63 [32]. In addition, Popescu indicated that patients with only TL were more likely to be women despite the fact that patients with TL and additional tissue infection were mostly men.

Living in high-burden or low-burden areas and social-economical conditions affect not only tuberculosis and EPTB but also TL rates as well. T. Gow Brown discussed the effects of living in an unhealthy environment and stated all manifestations of tuberculosis to be increased under unhealthy conditions [12]. Unfavourable environment and disadvantaged status also move the peak incidence of TL towards childhood.

Coexistence of an immunosuppressive condition significantly increases all extrapulmonary manifestations as well as TL. In a study in Brazil, Teresa Gomes found EPTB cases to be nearly doubled when compared to the cases without comorbidities [14]. A meta-analysis performed by Naing C et al. demonstrated the significant association between HIV and EPTB. HIV-related immunosuppression not only affects the clinical presentation of TB but also increases the frequency of EPTB as well [26]. Fifty-three to sixty-three percent of HIV-infected patients tend to have isolated EPTB [1].

5.2 Pathogenesis

Mycobacterium tuberculosis targets mainly the lungs, but dissemination to other organ is not rare. Lymphatic tissue is the most frequent extrapulmonary destination for mycobacterium. Bacilli infecting the lymph nodes may spread to the tissue via lymphatics or haematogenous dissemination from the primary source in the body, with contact with an open wound, or by alimentary tract.

Upon surpassing primary defence mechanisms of the upper respiratory tract and gaining access to the alveoli, the bacilli are engulfed by alveolar macrophages. Normally soon after phagocytosed by macrophages, many bacteria are exterminated inside the cell by fusion of lytic enzyme-filled lysosomes and phagosome. Mycobacterium tuberculosis, instead of extermination via fusion of phagosome and lysosome, outpasses this step with its various surface molecules interacting with the primary defence system and proliferates either in the phagosome or inside the cytoplasm until leaving the macrophage. Researches indicate that the cellular immune defence, antigen-specific T cell activation against tuberculosis, initiates soon after the bacteria reaches to the draining lymph node and dendritic cells play an important role in this dissemination [7, 11, 20, 44].

On the other hand, *Mycobacterium tuberculosis* is a slow-growing microorganism. Presentation of the bacteria to the draining lymph node by dendritic cells does not occur until the bacteria reaches to a sufficient amount to be recognized and presented. Later, upon presentation of the bacteria to the draining lymph nodes, effector T lymphocytes start to differentiate, and cellular defence takes place by migration of these effector T lymphocytes to the infected area. Thus, it is not surprising that the lymph nodes are the most common site of extrapulmonary tuberculous infection.

In addition, the affecting bacteria does not always reach to the lymph nodes after inhalation. Another mycobacterium species, *Mycobacterium bovis*, may be digested

orally and cause especially cervical and abdominal lymphadenitis. Cervical lymphadenitis due to *Mycobacterium bovis* represents a great vast of cases in countries where animals are infected with the bacteria and milk of these animals is consumed without pasteurisation.

5.3 Clinical Presentation

Depending on the subspecies of *Mycobacterium*, TL affects cervical-supraclavicular, mediastinal, axillary and inguinal lymph nodes with the order of frequency. The percentage of the involved cervical lymph nodes vary between percentages of 63% and 77% [13, 23]. Hence, clinical descriptions and symptomatology mostly described over cervical TL. Patients mostly complains of painless and slowly enlarging lymph nodes at the posterior cervical or supraclavicular region. Thus, patients show lymph node hyperplasia with unresponsiveness to antibiotics, especially from an endemic area, must be evaluated for TL.

Madegedara et al. with a study from an endemic area, Sri Lanka, analysed the frequency of affected lymph nodes in a group of 152 patients with isolated EPTB, and results are shown in the table below.

Site of aspiration	Percentage %
Cervical	78.94
Axillary	11.18
Cervical and axillary	3.28
Submandibular	3.28
Supraclavicular	1.31
Inguinal	1.31
Inguinal and axillary	0.66

Systemic symptomatology includes a low-grade fever, fatigue and weight loss. However, young children and immunocompromised HIV-positive patients may develop significant fever and rapidly enlarging lymph nodes [4].

Hyperplasia is the first reaction of the infected lymphatic tissue and occurs within weeks or months of duration. Development of a granuloma takes place gradually. The lymph node is firm, mobile and discrete initially and in time attaches to the surrounding tissue. Drainage from the swollen lymphatic tissue may occur in around 10% of cases [18, 23]. Usually, more than one lymph node at the area are involved, but one of them is prominent among others and is enlarged asymmetrically. Necrotic caseation gradually occurs in the affected lymph node. Eventually, following necrosis, the affected lymph node comprises a liquid content and starts to fluctuate. Later on, the content of the lymph node may drain freely through a formed track. The drainage may persist for months.

The swollen lymph node may resist and form ‘cold abscess’ despite adequate medication. Coinfection with other bacteria causes peri-lymphadenitis and other signs of inflammation; fever, colour change and pain occur [38].

Patients having concomitant TL and pulmonary tuberculosis will complain of classical tuberculosis symptoms consisting of coughing up blood, chest pain, unintentional weight loss, fatigue, fever, night sweats and chills. Accompanying HIV and childhood also increase the presence of concomitant constitutional tuberculosis symptoms.

A retrospective study performed by Popescu et al. determined that not a single LN but a lymph node group is involved in almost all patients. Besides, in the same study, it is concluded that a single lymph node association is much more common than multiple lymph nodes to be affected. As far, multiple lymph node involvement, matting enlargement and caseating necrosis are the main clinical findings in TL.

As the cervical lymph nodes are the most common group to be affected by TL, observing the clinical changes of LN is easier. In order to suspect clinically from TL, a five-stage classification of TL by Jones and Campbell in 1962 will be helpful to recognise the disease.

(i) Stage 1, enlarged, firm, mobile, discrete nodes showing non-specific hyperplasia
(ii) Stage 2, large rubbery nodes fixed to surround tissue owing to periadenitis
(iii) Stage 3, central softening due to abscess formation
(iv) Stage 4, collar-stud abscess formation
(v) Stage 5, sinus tract formation

Clinically, it is easy to observe TL while located at anatomically visible locations, but suspicion of TL is more challenging while located at other lymph node groups. Clinical signs at these cases depend on the blockage of lymphatic drainage of the area and compression effect on the surrounding structures.

Mediastinal TL: A distressing cough and chest pain may be the leading symptom of the mediastinal disease. However, compression of the neighbouring tissue may also develop signs for lymphadenomegaly. Patients may have atelectasis or positional dyspnea due to compression of one of the lungs, dysphagia due to oesophagal compression [36, 45] or cardiac tamponade [29]. Oesophagal perforation and fistula formation between the oesophagus and trachea also have been reported [27].

Axillary TL: Without existing pulmonary tuberculosis, patients may develop painless, gradually enlarging axillary mass. Blockage of lymphatic drainage and swelling of the preceding tissue may present.

Peritoneal TL: Periportal, peripancreatic and mesenteric lymph nodes are frequently involved [34]. Baik SJ et al. reported a case of obstructive jaundice caused by pericholedocal tuberculous lymphadenitis [3].

5.4 Diagnosis

Being mostly localised in a visible area makes it easy for suspicion for tuberculosis. However, putting the right diagnosis is still challenging. At an endemic area for TB, patients with lymphadenitis should be carefully questioned for contact with TB positive individuals, previous TB history, living environment, constitutional symptoms, concomitant diseases especially HIV, duration of the swelling and the change in the character of the swelling in time. With the suspicion, laboratory confirmation is essential. However, none of the laboratory tests are hundred per cent certain to exclude the disease.

(a) Mantoux test (Tuberculin Skin Test): Mantoux test remains a valuable test in diagnosing tuberculous diseases especially latent tuberculosis cases. The initial step for the test is the intradermal injection of five tuberculin unit (TU) (0.1 mL) of purified protein derivative to an area of the forearm without hair and measuring the size of the induration 48–72 h later. The need for a second visit of the patient and the challenges of interpreting the results due to prior vaccination are negative aspects of the test. Although it has difficulties with the application, Lakhey M emphasized the value of Mantoux test with a study consisted of 122 TL cases, concluding that the combination of cytology, staining and Mantoux test enhances the diagnostic efficiency [21].

(b) Acid-fast staining, Erlich-Ziehl-Neelsen stain (EZN): While having a concomitant pulmonary active tuberculosis, there is more chance to identify the bacteria with the classical acid-fast staining (AFS) method. However, a high load of bacteria, approximately over 1000 per mL, is needed to successfully determine the bacteria. Although the bacterial load is important for a positive result for EZN staining, the overall sensitivity is reported as 71.4% for pulmonary specimens and 24% for extrapulmonary specimens [19]. Additionally, collections obtained from a draining fistula, or other clinical specimens from the LNs, are valuable for investigation, and a positive EZN result is highly specific for tuberculous infection but still has false-positive and false-negative results.

(c) Histopathology: Histopathologically investigation of the specimen from the affected LN gives highly specific results. Material from the affected lymph may be collected in several ways. First of all, fine needle aspiration (FNA) is less invasive and easier. Depending on the location of the affected LN, aspiration may be performed with a simple syringe or with the use of complex techniques such as bronchoscopy or gastroscopy. In some clinical circumstances such as a firm and solid mass which it is not possible to aspirate, an excisional biopsy was performed in order to fully take out the swollen LN. The specimens obtained by either method are valuable for EZN staining, bacterial culture, rapid tests and histopathological examination. Lymphoid infiltrate, noncaseating granulomas and caseification inside the granuloma with Langerhans giant cells are histological indicators for TL. Although FNA is less invasive than an excisional biopsy, various studies concluded that excisional biopsy has greater value to determine TL [22, 31, 35].

(d) Bacterial culture: Growth of the bacteria on culture media is the gold standard for the diagnosis of tuberculosis. However, the growth in the media is slow (usually requires 2–4 weeks), and a negative culture result does not exclude the disease. The specimens obtained from the affected LN, especially by excisional biopsy, have the highest diagnostic value. Sputum or blood cultures may also be helpful.

(e) Polymerase chain reaction (PCR): It is widely available in developed and developing countries. Aljaferi et al. published a study in 2004 which concluded that PCR is a faster and a reliable test in the immediate characterisation of *Mycobacterium tuberculosis* in 96.2% cases included in the study [2].

(f) Nucleic acid amplification tests (NAATs): There are commercially available NAATs; Amplified Mycobacterium tuberculosis direct test (MTD, Gen-Probe), Xpert MTB/RIF (often called GeneXpert)), pyrosequencing and homebrews.

  (i) Gen-Probe MTD test is the first NAAT announced and approved by FDA for AFB-positive patients. Later in 1999, Enhanced MTD (E-MTD) was approved also for AFB negative patients. The test principle is transcription-mediated amplification and targets ribosomal RNA of *Mycobacterium tuberculosis*. Its sensitivity is over 70% and significantly increases in AFB-positive cases. Specificity for the test is 98%.

  (ii) Xpert MTB/RIF was approved by FDA in 2013 for detection of *Mycobacterium tuberculosis* in all types of clinical specimens. The test has higher sensitivity in high-burden countries, and it also tests the rifampicin resistance. Chang et al. made a meta-analysis using drug susceptibility tests and cultures as the gold standard and published the sensitivity and specificity of the test as 95% and 98%, respectively [9]. Other advantages of the test are being automated cartridge-based, eliminated contamination and fast results. The results may be obtained in less than 2 h.

  (iii) Pyrosequencing (PSQ) is also another NAAT and often used to detect mutations responsible for drug resistance. PSQ can be used on specimens which are AFB positive and tests for rıfampin, INH and quinolone mutations.

  (iv) HAIN is a line probe assay which is not yet approved by the FDA but detects INH, rifampin and quinolone resistance.

(g) Imaging: Depending on the localisation of the affected LN, imaging techniques may alternate.

  (i) Chest X-ray is the first imaging technique for tuberculosis. It is easily accessible, cheap and successful in displaying the calcification; thus it still remains as one of the first-order studies for diagnosing pulmonary tuberculosis. But ultrasonography is more convenient in TL.

  (ii) Ultrasonography: because of being mostly localized at cervical lymph nodes, USG is beneficial for defining the amount of the lymph nodes involved, shape and boards, matting, measuring the size of the lymph nodes and exploring whether there is adjacent soft tissue oedema.

Surrounding soft tissue oedema, necrosis inside the lymph node, matting and posterior improvement are in favouring criteria for TL against metastatic lymph node enlargement [47]. Upon the development of necrosis, the homogenous structure of the lymph node changes, and the centre may be visualised as a heterogeneous area. Additionally USG maybe helpful with guiding FNA from the lymph node.

(iii) CT and MRI are valuable tests in diagnosing TL. The ability to show the anatomical structures and the relationship of the affected lymph nodes with the adjacent tissue with a 3D model and to demonstrate central necrosis as weakened signals on CT and hyperintense on T2 MR images are the favourable specifications for the methods ([39]). Besides, CT is the best choice for evaluating abdominal lymph node tuberculosis. But distinguishing the necrosis of TB and squamous cell ca is still difficult with these methods. Due to high radioactivity, CT will not be the first choice in demonstrating lymph node; besides, in order to visualise the calcified centre, IV contrast, which may be toxic to the patient, will be needed. Although it is expensive and not available in many facilities, MRI can replace CT under these conditions.

(iv) PET-CT is a method generally used for investigation of tumour metastasis. Expensive, time-consuming and hardly found in most facilities. The value of diagnostic studies for TL is still controversial. However, it may be beneficial in differentiating some patterns of pulmonary tuberculosis like pulmonary and lymphatic pattern (Soussan et al) [37]. Additionally, some researchers reported PET-CT to be useful for following the response to antituberculous therapy [40, 46].

(h) Laboratory

(i) ESR is usually elevated but is not specific for TL.

(ii) IFN-gamma release assays (IGRAs): *Mycobacterium tuberculosis* differs from most other environmental mycobacteria and attenuated *Mycobacterium tuberculosis* which is known as Bacillus Calmette Guerin (BCG) and used for vaccination worldwide against tuberculosis. The difference in the genome is called 'Region of Difference' (RD1). The RD1 area encodes for nine proteins. The main principle of the method is to determine the presence of RD1 in suspected patients. White blood cells of persons infected by *Mycobacterium tuberculosis* will release IFN gamma when mixed with antigens. The presence of RD1 clinically indicates *Mycobacterium tuberculosis* infection, and the test is negative in patients who are vaccinated with BCG and infected by environmental mycobacteria. The two IGRAs approved by FDA are QuantiFERON-TB Gold In-Tube (QFT-GIT) test and T-SPOT TB test (T-Spot).

1. QuantiFERON-TB Gold In-Tube: ESAT-6, CFP-10 and TB7.7 are the three synthetic peptides as *Mycobacterium tuberculosis* antigens and are in a single mixture. IFN-gamma concentration is measured by the test.

2. T-SPOT TB test: Two proteins, ESAT6 and CFP10 of RD1, are used to activate T cells of the patient. Effector T cells that recognise the two proteins start to release IFN gamma.

One-day result and no need for a second visit are advantages of the IGRAs. However the high cost and required complex technique make the test less advisable for low-income countries; thus WHO does not only recommend IGRAs to replace Mantoux test but also disadvise to use for the diagnosis of active TB in low-income countries. CDC recommends the use of the tests as an aid in diagnosing *M. tuberculosis* infection with special conditions as contacted persons, pregnant and healthcare workers' screening (CDC fact sheets).

5.5 Differential Diagnosis

Although a vast majority of lymph node enlargements especially in high-burden countries are etiologically TL, several other causes have to be kept in mind. As well as other infections of the lymph nodes (e.g. toxoplasmosis, bartonellosis, fungal infections, tularemia), primary lymph node malignancies (esp lymphoma) and metastases, autoimmune diseases, drug reactions and some other syndromes like sarcoidosis, cystic fibrosis and storage disorders must be kept in mind for differential diagnosis. A general diagnostic algorithm starting with a good history, well examination, FNA cytology and GeneXpert testing is advised to be followed for the distinction of TL.

5.6 Treatment

Determining the causative agent of lymphadenitis and drug resistance is crucial for the choice of treatment. IDSA recommendations for TL caused by mycobacteria with no drug resistance are 2 months of isoniazid, rifampin, pyrazinamide and ethambutol and isoniazid and rifampin for the following 4 months [6].

During the treatment, a paradoxical lymph node enlargement, new lymph node involvement and a new draining sinus may occur. Paradoxical reactions may take place in 20%, 23% of HIV seronegative patients [10, 16]. In HIV-positive patients, with the contribution of antiretroviral therapy, it is more complicated to define paradoxical reactions.

Surgery is the first choice for nontuberculous lymphadenitis with cure rates over 70% [28]. In addition, surgical excision may be performed in patients with paradoxical reactions during therapy, patients who are not compliant with therapy and patients who feel uncomfortable with the existing lymph node enlargement or draining lymph node. However, antibiotic treatment is recommended even surgery is performed.

5.7 Follow-Up

Positive treatment criteria are the clinical improvement in symptoms and reduction in the size of a lymph node. Additionally, if needed, GeneXpert MTB test is useful in following up the response for the treatment.

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Chapter 6
Tuberculosis Arthritis and Osteomyelitis

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6.1 Tuberculosis Arthritis

6.1.1 Epidemiology

Musculoskeletal tuberculosis (TB) is a rare extra-pulmonary complication of *Mycobacterium tuberculosis*. Osteoarticular tuberculosis is still a common problem in developing countries. All the cases should be questioned according to birth or resident area to state a country with high TB prevalence [1, 2]. Bone and joint TB infection is a secondary form of TB occurring most commonly due to hematogenous seeding by retrograde lymphatic and contiguous dissemination are the other less common spread from a primary focus such as the lung, kidney, or lymph node or, infrequently, through contiguous spread from adjacent tissues by direct inoculation [3]. About half of the cases involve spinal involvement and the rest involve extraspinal osteoarticular joints. Bone and joint tuberculosis accounts for 1–4.3% of all tuberculosis cases [4, 5] and 10–15% of all extrapulmonary tuberculosis cases, but the incidence of those cases has been rising due to the increasing number of immunosuppressed patients and HIV infections [5, 6]. Rarely, tenosynovitis, bursitis, or pyomyositis may occur at lower rates [7]. Commonly involved body areas are backbone and weight-bearing joints. On the other hand, joint tuberculosis may be due to direct invasion of the synovia, such as Poncet's arthritis [5, 7]. In addition, weight-bearing joints such as wrist, elbow, and the small joints of the hands may be involved. Results of joint diseases are periarticular demineralization, marginal

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erosion sites, and consequently a synovitis with impaired support structure [8]. Synovitis can be rapid in joint damage, especially in weight-bearing joints. If tuberculous tenosynovitis and arthritis become complicated due to a secondary infection such as *Staphylococcus aureus*, severe systemic symptoms and increased joint damage may be observed [5]. There is increased susceptibility to tuberculosis infection in patients with sickle cell disease and chondrocalcinosis at the bottom and other joint involvement and osteonecrosis. Additionally cases of tuberculous arthritis can be found in patients with Sjögren's syndrome, rheumatoid arthritis, seronegative arthropathies, gout, and Charcot arthropathy [5]. Immunosuppressive and/or glucocorticoids therapy, patients receiving anti-TNF therapy have suggested an increased incidence of joint infections.

Joint tuberculosis may cause severe deformation and loss of motion in the joint due to delayed diagnosis of TB in cases of low-endemic area and additional pathology [9]. TB of joints is most commonly monoarticular [5, 6]. Different findings have been reported in terms of age and gender predominance in different case series. In general TB arthritis is more common in children [5]. However Enache et al. found in a 10-year case report that 2/3 patients were over 40 years of age [10]. Two studies reported 50 and 60 years; in that study, the rate of female was generally more dominant; on the other hand, in some study it has been found that a bone joint involvement is more common in men [5, 7, 11].

6.1.2 Clinical Feature and Diagnosis

Granulomatous changes and cartilage erosion cause chronic effusion and progressive joint damage. Findings of acute inflammation are rarely seen; local deformity and movement restriction are more frequently observed. The most common symptom is chronic joint pain; it may be only minimal signs of inflammation [9]. In some cases, local swelling and a sinus tract can be seen as additional [5]. Monoarticular arthritis is common in case of joint tuberculosis [5, 6]. Strong night pain can be encountered in TB of hip and knee joints and wasting of the regional muscle, and some deformities may occur. Systemic symptoms of fever, weight loss, and night sweats may or may not be present during active TB tenosynovitis and arthritis. Less than 50% of individuals with tubercular tenosynovitis and arthritis have active pulmonary TB, but negative results do not exclude diagnosis [12]. Although imaging features of joints and tendons TB X-ray features have been generally found nonspecific, a painless cold abscess may be reported as the only clinical presentation less common [8, 12]. Radiographic features are usually recognized 2–5 months after the onset of the disease [5, 13]. The classic triple of TB tenosynovitis and arthritis (Phemister's triad) are juxta-articular osteoporosis, peripheral bone erosion, and intra-articular space narrowing gradually in the radiological features [2, 14]. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful for further identification of the disease [15–17]. MRI better defines soft tissues infections, and CT is better for bone lesions. MRI features of tuberculous

tenosynovitis and arthritis include synovitis, effusion, central and peripheral erosions, active and chronic pannus, abscess, bone fractures, and hypo-intensive synovia. MR is the preferred investigation to reveal the degree of the disease and severity of the damage [15]. MR is also non-specific but better describes the width of the lesion when compared to X-rays. These imaging features may help to diagnose tuberculous tenosynovitis and arthritis in an appropriate clinical setting [15, 18].

Severe clinical suspicion is required. In the case series by Enache et al., clinically delayed due to the absence of specific clinical findings were found as 26% and cause a delay in diagnosis of joint TB infection [6, 10]. On the other hand, on a retrospective evaluation, clinically suggestive findings were found in only 26% of joint TB infections.

Clinically, TB tenosynovitis and arthritis are evaluated at five stages [15, 19]:

- Stage I or synovitis: tissue edema, bone lesions, and localized osteoporosis are present, and the outcome of the treatment is excellent.
- Stage II results in early arthritis with marginal erosions (one or more erosions or lytic lesions in the bone, reduced joint space) and mild joint stiffness.
- Stage III is advanced stage arthritis with cyst formation and loss of joint space; the result is a serious loss of motion.
- Stage IV is arthritis at a more advanced level with limited joint disruption and post-joint therapy and limited mobility.
- Stage V is ankylosis of the joint.

General laboratory findings are also neither specific nor reliable. Raised ESR has been observed [5]. PPD has a limited role in adults in high prevalence area but can be useful in children under 5 years.

Synovial fluid aspiration: Synovial fluid is usually nonhemorrhagic, with moderate elevation of the white blood cell count, below 50.000 cells/mL with a predominance of polymorphonuclear leukocytes or lymphocytes. AFB smear and culture for *M. tuberculosis* should also be planned. A direct smear of synovial fluid or operative specimen can show positivity for AFB in as low as 27% of cases [6]. During AFB investigation, it is recommended to obtain at least two, preferably three, samples, and if the bacteria are more than 10,000 per ml in the sample, AFB can be revealed. Different culture methods such as Lowestein-Jensen medium and radiometric (Bactec 12B fluid medium) and non-radiometric (Bactec MGIT 960 system) culture can be used to confirm in the paucibacillary state [15].

Diagnosis can be classified into three categories [5]:

1. Definitive confirmed TB diagnosis – had positive culture
2. Suspected TB – had positive AFB smear/chronic granulomatous inflammation
3. Possible TB – favorable radiological and clinical response to antituberculosis treatment

Culture is the gold standard, and the specimens t are biopsy specimen, aspiration from joint space, or sinus tract specimen should be examined by AFB smear and histopathologic method as well as cultures [5, 6]. Generally culture positivity has been found low percentages. In this situation, histological evaluation is one of the

important diagnostic tests. Biopsy of bony lesion/synovium/soft tissue masses may help to clear up diagnostic confusion [6, 20]. Possibly diagnosed patient in area of high prevalence with limited resources can be treated by clinical features, and X-ray suggests without biopsy. If a case is unresponsive to chemotherapy, and there is suspicion of resistant infection or other diseases, a synovial biopsy is recommended [5]. The most important findings of histologic evaluation are epithelioid granulomas and caseous necrosis. In some cases TB PCR positivity can be leading non-specific granulomatous response [5, 10]. PCR technique can increase the sensitivity and help exclude non-tuberculous mycobacterial infection of soft tissue [6]. Diagnostic rate of PRC is reported 33.3% in a study [7]. In the case of elbow joint TB reported by Sagoo et al., when initial treatment did not bring complete relief, a synovial biopsy with debridement was done (along with smear, culture and PCR) [8]. This could be a good approach to diagnosis but expensive and complex and may not always be practicable.

Early diagnosis of osteoarticular TB is important to prevent advanced destruction of the joint and bone structure and suffering from systemic spreading infection.

The tuberculin skin test (TST) is recommended standardly, but sensitivity and specificity are known to be low. If the prevalence of TB infection were high, the positive predictive value of TST would be higher [21]. In additionally interferon-gamma release assays (IGRAs) are blood-based assays that have recently become available and have good diagnostic values for chronic inflammatory arthritis; however, indeterminate results may be difficult to use of them [22].

6.1.3 Management and Treatment

Splints can be used briefly to reduce acute symptoms or can be used for long periods in selected cases to prevent deformities of the infected extremities and joints [15, 23]. Surgical treatment is usually limited and does not require, except biopsy to obtain infected tissue, open or arthroscopic debridement, abscess drainage, and synovectomy [15]. However, surgery appears to be beneficial and may be indicated. Such situations include failure to respond to chemotherapy with evidence of ongoing infection, the patients with persistent of recurrence of neurological complications. It is not recommended that surgical procedures should be performed in the joints with severe cartilage destruction, deformities, large abscess, and multidrug-resistant TB [15, 24].

Antituberculosis treatment is a multidrug complex [5]. The results of appropriate treatment are good with low morbidity and mortality. Even in the advanced cases, good response can be seen. Early antimicrobial therapy provides near-complete cure and preservation of function. Antituberculosis therapy in general should be of at least 9–12 months but to be continued longer in children and immunocompromised hosts [3, 12]. The basic principles for the treatment of pulmonary tuberculosis are also applied for extrapulmonary disease [13]. Two months of isoniazid (INH)

and rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) followed by 7–10 months of INH and RIF are recommended as an initial therapy unless the organisms are known or strongly suspected resistant TB to the first-line drugs.

6.1.4 Special Joint Infections

Prosthetic joint infection (PJI) due to *M. tuberculosis* is rare and was reported as case in few studies [25, 26]. A misdiagnosed patient has knee or hip osteoarthritis after joint arthroplasty, with culture negativity [26]. The diagnosis is often difficult and should be suspected in culture-negative PJI with histological features of granulomatous lesions with or without caseous necrosis. The diagnosis may be confirmed by isolation of the microorganism on Löwenstein culture or by molecular techniques (PCR). Resection arthroplasty or arthrodesis has been used to treat of PJI, but when there is no loosening of the prosthesis, the patient may cure with debridement, exchange of the polyethylene components while retaining the prosthesis, and prolonged antituberculous therapy (9–12 months).

Multifocal osteoarticular tuberculosis Four to six bones or joints are affected, and there are some cases that have more focus. It occurs mostly in the hands and feet of flat bones in children and may also have spinal involvement [25]. Whole body scintigraphy may be useful in detecting lesions in different regions. Although the duration of antituberculosis treatment in clinical features is not known due to this uncommon bone involvement, most patients are treated for 24 months.

Tuberculous sacroiliitis The sacroiliac joint is affected in 4–9.5% of patients. The diagnosis cannot be delayed (92%). Tuberculous sacroiliitis may be confused by septic arthritis, inflammatory diseases (such as rheumatoid arthritis), ankylosing spondylitis and Reiter's disease, gut and pseudograft, tumorlike conditions (e.g., pigmented villonodular synovitis), and endemic that may be miscible with the brucella sacroiliitis in the regions [25]. Arthrodesis is used in patients with large periarticular apse and persistent aches. Treatment of this involvement requires 6–9 months of antibiotic therapy.

6.2 Tuberculosis Osteomyelitis

6.2.1 Epidemiology

Tuberculosis osteomyelitis accounts approximately 10% of all extrapulmonary TB cases and is the third most common type of extrapulmonary TB after pleural and lymphatic disease. The presentation of TB may be insidious over a long period, and the diagnosis may be elusive and delayed. The diagnosis is often confused with

malignancy [27]. In a series of 194 patients from India with TB, 30% of cases occurred during the second decade of life, 22% in the first decade, 18% in the third decade, and 14% in the fourth decade [5]. Tuberculosis osteomyelitis shows a bimodal age distribution: in developed countries, the disease commonly affects people older than 55 years, whereas in immigrants, it is more common in younger individuals (20–35 years old). In patients with skeletal tuberculosis, concomitant pulmonary involvement is diagnosed in 6.9–29% of cases [28].

6.2.2 Pathophysiology

Tuberculous osteomyelitis pathophysiology generally arises from reactivation of bacilli lodged in bone during the original mycobacteria primary infection. In adults, the lesion may be single and affect any bone, including long bones, the pelvis, ribs, and skull. In children, multiple lesions in long bones dominate, but the bones of the hands and feet may be affected.

The tendency of the bacillus for the spine and large joints can be explained by the rich vascular supply of the vertebra and growth plates of the long bones. Tuberculous arthritis is believed to result from extension of an initial infectious focus in the bone to the joint. Infrequently, tuberculous bacilli travel from the lung to the spine along the Batson paravertebral venous plexus or by lymphatic drainage to the para-aortic lymph node [29].

Osteoarticular lesions result from hematogenous spread of a primary infection. Any bone, joint, or bursa can be infected, but the spine, hip, and knee are the preferred sites of infection, representing 70–80% of infections [30]. Hematogenous dissemination can occur in immunocompromised patients with bone infections, such as individuals with AIDS or transplant recipients [25].

The growth plates (metaphyses) receive the richest blood supply and are most often the initial site of infection. Tubercle bacilli invade the end arteries, causing endarteritis and bone destruction through the epiphysis. After crossing the epiphysis, bacilli can drain into the joint space, resulting in tuberculous arthritis, or form a sinus tract after being released from the destroyed bone. *M. tuberculosis* does not produce any cartilage destroying enzymes as are seen in pyogenic infections.

A closed cystic form of skeletal TB can occur, especially in the long bones, and may not have associated sclerosis, osteopenia, or abscess/sinus tract formation as in other forms of skeletal TB. This form of TB is more likely to occur in children and may be misdiagnosed as a malignancy.

If the infection progresses without treatment, abscesses surrounding the joint or bone may develop. These are often described as being “cold” abscesses. Calcifications are also frequently seen in healed lesions. As the area of infection enlarges, the center becomes necrotic, resulting in an area of caseating necrosis. This caseation may progress to cause bone expansion and eventually destruction of the cortex. A pathological feature of tuberculous osteomyelitis is that there is usually no bone regeneration (sclerosis) or periosteal reaction.

Although uncommon, TB can also involve the ribs and skull. The skull contains little cancellous bone, which is usually affected by *M. tuberculosis*. Disease involving the skull occurs more often in children and anecdotally may be associated with head trauma [31].

Several reports have noted an association between mechanical factors such as trauma and the development of skeletal TB. In a Canadian study of 99 patients with skeletal TB, 30 had a history of trauma preceding their presentation and 7 had a recent history of intra-articular steroid injection. This may also explain why weight-bearing joints are most frequently involved. Trauma may be associated with skeletal TB because of resulting increased vascularity, decreased resistance, or unmasking of latent infection [32].

6.2.3 Clinical Feature and Diagnosis

Tuberculous osteomyelitis often occurs in conjunction with tuberculous arthritis, but it can occur as a distinct entity without joint involvement. In adults, tuberculous osteomyelitis without joint involvement usually presents as a single lesion, usually in the metaphysis of long bones (e.g., femur and humerus), although the ribs, pelvis, skull, mastoid, and mandible can be affected. In children, older adults, and immunocompromised persons, including those with HIV infection, the lesions may be multiple [33]. In children, the lesions may affect the short bones of the hands and feet; tuberculous dactylitis has been reported to occur in adults but is unusual. Patients with widespread lesions may be misdiagnosed as having a malignant process [34]. Bacterial superinfection can also mask the diagnosis and presentation, as there are reports of infection due to coexisting *Staphylococcus aureus* infection and TB [35]. Tuberculous osteomyelitis usually manifests with pain and swelling adjacent to the bone, with eventual limitation of movement of the affected limb. Symptoms may be present for 6–24 months before a diagnosis is made. Fever, weight loss, and night sweats are often present. Abscesses and sinus tracts may occur, often later in the course [36]. Tuberculous involvement of the skull may be associated with headaches and soft tissue masses. TB involving the ribs manifests with chest pain and sometimes with a “cold” chest wall mass. Infection of bones of the head and neck, especially the mastoid and mandible, has been reported to result from tuberculous otitis and disease involving the oral cavity. Facial paralysis can occur secondarily to tuberculous mastoiditis [37]. TB of the temporomandibular joint has also been reported as a cause of chronic temporomandibular joint pain [38]. TB of the sternum can manifest as anterior chest pain [39].

A high index of suspicion is needed for the diagnosis of TB, especially given the insidious onset of symptoms and reports of a long duration between onset of symptoms and diagnosis of disease. In countries with a high burden of TB disease, musculoskeletal complaints may be attributed to TB correctly based on clinical and radiologic examination. In the developed world with a lower incidence of TB, the diagnosis may not be initially considered, and the diagnosis is frequently delayed.

Any bone or joint may be involved, but the spine and weight-bearing joints are the most common sites of infection. Pain is the most common complaint that leads a patient to seek medical care, and TB should be considered in the differential diagnosis of the cause of skeletal pain. Interestingly, local pain, swelling, and limitation of movement may even on occasion precede radiographic findings by up to 8 weeks [40]. Cold abscesses can occur and sometimes with draining sinus tracts, but this is usually seen in advanced, untreated disease or among patients with HIV infection. The differential diagnosis of tuberculosis osteomyelitis includes other infectious causes of musculoskeletal disease (bacterial, fungal, and other mycobacterial pathogens), as well as malignancy, rheumatologic conditions, and sarcoidosis. Imaging techniques, which include conventional radiography, CT, and MRI, are useful in evaluation of patients with suspected tuberculosis osteomyelitis and other skeletal diseases. The use of newer techniques such as CT, MRI, and CT-guided fine-needle aspiration biopsy has revolutionized the diagnostic approach and has resulted in more accurate results and much less invasive procedures than when only plain radiography and open biopsy were available [15]. Previously, conventional radiography had been the mainstay in the diagnosis of tuberculous osteomyelitis.

Since there are no pathognomonic radiographic findings, the diagnosis is usually made by tissue biopsy and/or culture [41]. Needle aspiration and biopsy can confirm the diagnosis with the findings of caseating granuloma and the presence of acid-fast bacilli (AFB) [5]. A positive culture for *M. tuberculosis* provides definitive evidence of tuberculous disease and allows antimicrobial susceptibility testing to be performed, which is essential for helping to prescribe optimal therapy. Fine-needle aspiration biopsy of involved bone (often CT directed) to obtain specimens for culture is useful diagnostically [42]. In addition to modern culture techniques performed on specimens obtained by biopsy of involved tissues, the use of molecular diagnostics to detect the presence of *M. tuberculosis* has the potential to improve the ability to diagnose skeletal and other types of musculoskeletal TB. While nucleic acid amplification for AFB smear-positive respiratory specimens, there are limited data on the utility of these tests for extrapulmonary TB [43]. This is especially the case for the use of these molecular diagnostic tests for tuberculosis osteomyelitis. The currently commercially available and FDA-approved nucleic acid amplification tests are not approved for use in extrapulmonary TB, including tuberculosis osteomyelitis. While further data are needed on the utility of these tests in the aid of diagnosis of tuberculosis osteomyelitis, recent reports from South Africa appear promising and suggest that Xpert MTB/RIF may be a valuable diagnostic test for tuberculosis osteomyelitis in both adults and children [44].

Recent TB diagnostic guidelines published by the American Thoracic Society, Infectious Diseases Society of America, and CDC suggest that the quality of data for the utility of nucleic acid amplification tests performed on specimens from patients with suspected extrapulmonary TB is low: the test results are specific but may lack sensitivity [45]. This suggests that a positive Xpert MTB/RIF is valuable but that a negative test does not rule out extrapulmonary TB. Radiographically, tuberculous osteomyelitis is often confused with malignancy, especially if the lesions are diffuse and lytic. Plain radiographs may show osteoporosis, lytic lesions,

sclerosis, and periostitis. Sequestra may appear as spicules of increased radiodensity within the area of destruction. Cystic lesions may be seen, especially in children and young adults. The lesions in children are less well defined than in adults, in whom well-defined margins of sclerosis are usually present [5]. Multifocal disease is an uncommon presentation and occurs primarily in children and the immunocompromised [46]. MRI is useful in detecting osteomyelitis early because of changes in the bone marrow. Tuberculous lesions are rarely seen in the hands and feet, but tuberculous dactylitis occurring in children is a well-recognized entity. The typical radiologic appearance is a ballooned-out configuration of "spina ventosa" in which the dissolution of bone causes absorption of trabeculae and expansion of the affected digit [47].

6.2.4 Management and Treatment

There are no controlled trials assessing treatment of tuberculosis osteomyelitis. Based on experience from treating tuberculous spondylitis and the experience with treating other forms of extrapulmonary disease, it is recommended that treatment of drug-susceptible tuberculous osteomyelitis be carried out using rifampin-based short-course regimens like those that are used for the treatment of pulmonary disease. Surgery is generally reserved for diagnosis and when necessary to drain an abscess that is not responding to medical therapy or to drain a large abscess to relieve pressure. Curettage and bone grafting followed by medical therapy yields good result [48]. Late treatment or inadequate treatment results in ankylosis of the affected joint by fibrosis or bony fusion. There are no formal recommendations, but some experts have suggested that patients requiring total arthroplasty for quiescent TB receive perioperative chemotherapy for at least 3 weeks before and at least 6–9 months after surgery to minimize the risk of reactivation. A total of 6–9 months of a rifampin-based regimen, like treatment of pulmonary TB, is recommended for the treatment of drug susceptible musculoskeletal disease.

6.3 Conclusions

Osteoarticular tuberculosis is a very rare form of tuberculosis. It is estimated that osteoarticular TB constitutes about 1.7–2% of all TB cases [49]. The rarity of the disease makes the general physician less aware of its presentation. Therefore, it is essential to educate and increase awareness of all physicians of the presentation of this disease in order to diagnose this disease promptly. Prompt diagnosis and treatment are important to avoid the development of skeletal deformities and finally long-term functional disabilities. The introduction of newer imaging modalities, including MRI and CT, has enhanced the diagnostic evaluation of patients with osteoarticular tuberculosis and for directed biopsies of affected areas of the

musculoskeletal system. Obtaining appropriate specimens for culture and other diagnostic tests are essential to establish a definitive diagnosis and recover *M. tuberculosis* for susceptibility testing.

Positive microbiological and histological yields can be obtained in 64–90% of all patients. Studies have shown that microbiological testing is less sensitive than the importance of biopsy [50]. In conclusion, it is important to have a high index of clinical suspicion of tuberculosis osteomyelitis and arthritis affecting any parts of the body. Patients suspected of having osteoarticular tuberculosis should be thoroughly investigated, and biopsy should be done if necessary.

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Chapter 7
Tuberculous Spondylodiscitis

Ayse Batirel

7.1 Introduction and Epidemiology

According to the global tuberculosis (TB) report 2016 of the World Health Organization (WHO) (http://www.who.int/tb/publications/global_report/gtbr2016_executive_summary.pdf?ua=1), the number of the estimated new TB cases worldwide was 10.4 million (56% of them were men), and the estimated number of deaths due to TB was 1.4 million in 2015. TB still remained among the top ten causes of death worldwide in the same year. "Tuberculous spondylodiscitis (TS)"/"spinal tuberculosis (ST)" and "Pott's disease" are synonyms which refer to the infection of the vertebral bones by *Mycobacterium tuberculosis*. Nontuberculous mycobacteria (NTM) rarely cause vertebral osteomyelitis [1, 2]. Before the description of tubercle bacillus by Robert Koch in 1882, Pott's disease was first defined by Sir Percivall Pott in 1779 based on the clinical presentation of a patient with spinal deformity and paraplegia [3]. Musculoskeletal TB accounts for approximately 10% of extrapulmonary TB cases and 1–5% of all TB cases [1, 4–6]. ST is the most common form of skeletal TB (accounts for about half of the cases) followed by tuberculous arthritis and extraspinal tuberculous osteomyelitis [7–10]. Male population is slightly more at risk of developing ST. More than half of the patients are men [11]. Mean age of the patients is 40–50 years (range: 8–60 years). In endemic areas, it occurs in younger subjects, whereas in non-endemic regions, it occurs mostly in adults [11, 12]. ST is endemic in most of the developing countries. During the 10-year period (from 2002 to 2011), the incidence of ST has significantly decreased in the

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USA. However, although it is not common, it still remains a public health issue [13]. In recent decades, its incidence – in context with the total TB incidence – in developed countries has been on the rise due to HIV-infected patients, immigrants from TB-endemic countries [11]. The incidence of ST among HIV-infected patients is comparable to that in HIV-uninfected patients [1, 12, 14]. The history of ST goes back to Egyptian mummies with lesions in skeletal bones. *Mycobacterium tuberculosis* complex DNA was detected in specimens from bone lesions of mummies [15–17].

It is a serious public health problem because the diagnosis of this destructive form of TB is usually delayed due to its indolent course. Delayed diagnosis and treatment result in permanent sequelae such as deformities and neurological deficits [1]. It is still an ongoing cause of mortality and morbidity in the twenty-first century despite advances in diagnostic tools and treatment [18].

7.2 Pathogenesis and Pathophysiology

Hematogenous seeding to bones occurs during the course of primary infection. Local adaptive immune responses play a role in the confinement of primary infectious foci. Contiguous spread from a primary focus or development of infection via lymphatic drainage is very rare. Predisposing conditions such as immunosuppression, advanced age, HIV infection, malnutrition, or chronic renal failure may lead to reactivation of latent infection in those foci in vertebral bones [19, 20]. Both osteomyelitis and arthritis occur in the context of ST. The initial site of infection by tubercle bacilli is the growth plate, followed by the inflammation of intervertebral joint, and then the infection spreads to involve the two adjacent vertebral bodies [21]. Invasion of end arteries leads to bone destruction. In case of contiguous involvement of the intervertebral disc as in so-called spondylodiscitis, vertebral collapse may take place. Sometimes, the avascular intervertebral disc is spared, in which case the term “spondylitis” is preferred. Cold abscesses around vertebral structures may develop. Drainage of the infectious focus into psoas muscle causes myositis and then psoas abscess may develop. Interferon-gamma, CD4+, and CD8+ T lymphocytes are the vital elements of the cellular immune response to TB [22]. Other than lymphocytes, epitheloid histiocytes, giant cells, plasma cells, and fibroblasts can be observed in histopathological specimens of the infected focus. Either exudative caseous necrosis destroys the bone tissue or granulation reaction occurs. Healing process usually happens with fibrous tissue formation and calcification. In contrast to pyogenic osteomyelitis, periosteal reaction or bone regeneration with sclerosis does not take place in ST [23]. Mostly, the anterior portion of the vertebral body is involved [24]. Collapse of the anterior parts of the vertebral bodies leads to “Gibbus deformity” (kyphosis associated with Pott’s disease). The thoracic and lumbar vertebrae are most commonly involved in ST [25, 26].

7.3 Clinical Manifestations

The clinical presentation is insidious and the early phase of the disease is indolent [1]. In a multinational, multicenter study including 314 patients with ST, the median duration from the onset of symptoms to diagnosis has been reported to be nearly 2.5 months [27]. In another study from Europe, the median duration of symptoms before diagnosis was 4 months [28]. The most common symptoms are back pain or pain in the involved area [12]. The severity of pain increases over time. Muscle spasm around the involved vertebrae may occur. Fever, weight loss, and night sweats are uncommon constitutional symptoms present in less than half of the patients, more commonly in advanced disease [29]. But, in the largest case series of 967 patients with ST reported from China, fever and night sweats were common presenting symptoms after back pain [26]. On physical examination, local tenderness over the spinous processes, severe pain induced by range of motion test, and in advanced cases kyphosis and neurologic symptoms such as numbness, tingling, weakness, and even paraplegia may be present. In the largest case series of 967 patients with ST from China, neurological involvement was present in 1/3 of the patients [26]. In another study conducted in France, half of the patients had neurologic symptoms and signs [28]. Wang H et al. have reported the frequencies of sensory and motor deficits as 54% and 28%, respectively, in their study including 329 patients with ST [30]. Neurologic deficit is usually reversible if early diagnosis and prompt treatment with urgent decompression can be performed at presentation [31]. Typical presentation of the disease includes back pain, gibbus deformity, paraplegia, or paraparesis. Atypical presentation involves epidural abscess without significant anterior vertebral involvement, noncontiguous multiple segments of the vertebral column, bilateral psoas abscesses, involvement of posterior segments of the vertebral column only, and sacral ST [32–34].

Thoracic vertebrae are the most commonly involved site, followed by lumbar and cervical spinal vertebrae in decreasing frequency [12]. In a large case series from Pakistan, the frequencies of the involved vertebral levels have been reported as dorsal spine (45%), followed by lumbosacral spine (33%), cervical spine (10%), and multiple levels (12%) [11]. Sharma A et al. have evaluated the clinical characteristics of 312 patients with ST. In their study, thoracic vertebrae were most commonly (46%) involved followed by thoracolumbar vertebrae (28%). In 80% of the patients, only one or two adjoining vertebrae were affected [35]. In immunocompromised patients (such as HIV-infected subjects) multiple vertebral lesions may be seen. NTM infection usually presents with widely spread lesions in the spine in older and/or immunosuppressed patients [36]. The most common NTM isolated as the cause of ST was *M. avium complex* (MAC) followed by *M. xenopi*, regardless of HIV infection. In HIV-infected patients, ST caused by NTM occurred at a younger age. Half of the patients with ST due to NTM had any form of immunosuppression, while 15% had a history of surgery or trauma. Surgery was indicated in 2/3 of those patients [37].

Table 7.1 Symptoms and signs of ST [1, 3, 27, 28]

	Frequency
Chronic back pain	58–87%
Local spinal tenderness	21%
Fever	31–48%
Weight loss	41–48%
Night sweats	18–49%
Cold abscesses Paraspinal Psoas	69% 59–63% 22–29%
Kyphosis/gibbus deformity	46%
Neurologic deficit	40–56%
Weakness of the lower extremities	69%
Paraplegia	10–25%
Spinal instability	21–33%

Neurologic symptoms develop early in the course of cervical ST [38]. Retropharyngeal abscess may the presenting sign of cervical ST [2, 39]. Tuberculin skin test (TST) was positive in ¾ of the patients with ST [27]. QuantiFERON(®)-TB Gold In-Tube test, which is an interferon-gamma releases assay (IGRA), was positive in 75% of patients [40]. Concomitant pulmonary TB has been reported in 3–14% of the cases [26, 27, 31]. Therefore, chest radiography is not useful for the diagnosis of ST. But it should always be obtained to rule out pulmonary tuberculosis which requires isolation of the patient with acido-resistant bacilli (ARB)-positive sputum production. Also, pulmonary involvement may facilitate the diagnosis of ST.

Because of delayed diagnosis, vertebral body collapse can lead to kyphosis or "Gibbus deformity" which is a form of structural kyphosis that may cause spinal cord compression. The cause of paraplegia is spinal cord compression either by gibbus deformity or osteophytes. Spinal cord compression may be present at the time of diagnosis in 40–70% of cases [41]. The most common complications of ST are paraplegia and quadriplegia depending on the nerve roots affected at the involved spinal level and spinal deformity (kyphosis or scoliosis). Compression fractures may also occur in untreated cases. Gibbus deformity causing spinal subluxation may cause such neurologic deficits due to spinal cord compression. If there is any motor deficit at the time of presentation, it is unlikely to recover completely despite therapy.

Paravertebral "cold abscess" (soft tissue mass) develops in most of the cases. Calcification of paravertebral abscesses may occur. Psoas muscles may be involved by spread of the infection [7]. *M. tuberculosis* is a quite common cause of psoas abscess in TB-endemic countries. In comparison to brucellar and pyogenic vertebral osteomyelitis, ST more commonly causes neurologic deficit, spinal deformity, and paravertebral abscesses. Also, thoracic vertebrae are more commonly involved in ST [42]. Involvement of noncontiguous multisegmental vertebrae without intervertebral discs is an atypical form of ST which is quite rare (3–16%) [11, 26, 27, 43, 44]. It may resemble malignant diseases [32, 44]. Symptoms and signs of ST and their frequency in patients diagnosed with ST are listed in Table 7.1.

7.4 Diagnosis

Because of the indolent presentation, the diagnosis is usually delayed. Prompt diagnosis is required to start appropriate therapy on time to prevent permanent sequelae development. Therefore, a high index of suspicion of ST based on epidemiological, past medical and/or contact history, clinical clues, and characteristic imaging findings is of paramount importance in earlier diagnosis [1, 12]. Especially in HIV-infected patients, no other symptoms or signs may be present. In TB-endemic countries, skeletal pain may lead to consideration of ST at initial presentation. However, in developed countries with low TB incidence, the diagnosis may be overlooked and delayed.

Imaging modalities [plain radiography, computed tomography (CT), and magnetic resonance imaging (MRI)] are useful tools to consider ST. Early in the course of the disease, radiography is not sensitive in diagnosis. Pathologic findings on radiography firstly occur in the anterior aspect of a vertebral body with reactive sclerosis, the vertebral end plate becomes demineralized [45]. Subsequent involvement of the adjacent vertebra leads to anterior wedging. Calcifications in abscesses can also be demonstrated on radiography [46]. But, radiography is not helpful early in the course of ST for diagnosis [47]. Bone sclerosis and destruction, lytic lesions and collapse of the intervertebral disc, destruction of the adjacent vertebral corpus, epidural extension (present in more than 60% of the patients), and calcifications of abscesses can be visualized on CT [48, 49]. CT can also be used as a guidance for FNAB and percutaneous drainage. Diagnostic yields of CT-guided bone biopsy for ST are 60–80% and were comparable to surgical biopsy [28, 50]. Specificities of CT-guided biopsy for pathogen detection were 83% and 91% in epidural infiltration and paravertebral abscesses, respectively [51].

MRI is the most sensitive imaging method in the diagnosis of ST. Destruction of the anterior portion of the vertebral body, anterior wedging, and paravertebral cold abscesses seen on MRI favor the diagnosis of ST [11, 46]. Contrast-enhanced MRI also reveals compression of the nerve roots or the spinal cord [52, 53]. MRI is superior to other imaging modalities in diagnosis of ST because of its high-contrast soft tissue resolution, imaging in multiple planes, and high sensitivity to detect early infiltration in bone marrow [11]. On T1-weighted images, hypointense vertebral bone marrow, reduced disc height, paraspinal soft tissue masses, and epidural extension of the inflammation can be demonstrated. On T2-weighted images, involved vertebral bodies, intervertebral discs, and soft tissues are seen as isointense or hyperintense areas [11]. Majority (85%) of the patients have typical MRI findings at presentation [35]. Epidural/paraspinal abscesses on MRI usually favor tuberculous spondylitis rather than pyogenic spondylitis [54, 55]. Radiographic features of ST are summarized in Table 7.2. MRI images of three different patients diagnosed with Pott's disease are shown in Figs. 7.1a–c, 7.2a, b, and 7.3a, b.

The diagnosis is established by microbiological and/or histopathological examination of the involved tissues and affected parts of the skeleton obtained by CT or ultrasound (US)-guided fine-needle aspiration and biopsy (FNAB) [52]. However, FNAB was inadequate for diagnosis in 27% of cases [56]. Microbiological

Table 7.2 Radiographic features of tuberculous spondylitis

Radiographic features
Involvement of adjacent vertebral bodies
Involvement of multiple vertebral levels
Demineralization of vertebral end plate
Lytic destruction of anterior portion of vertebral body
Sparing of the intervertebral disc Disc space narrowing due to disc destruction
Anterior wedging of vertebrae
Vertebral body collapse
Subligamentous spread of infection Paravertebral abscess
Psoas muscle involvement or abscess Heterogenous signal intensity and rim enhancement on MRI

Adapted from reference [42] and [46]

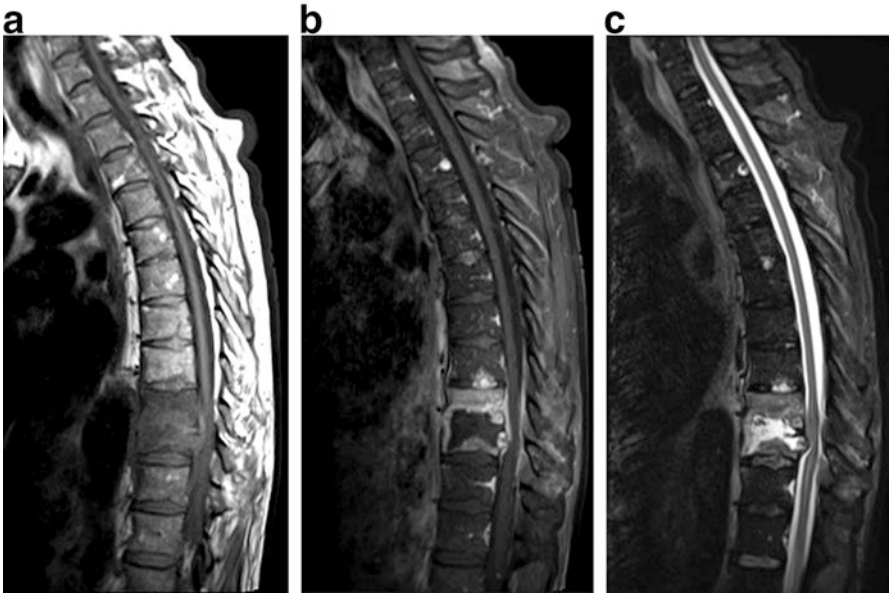

Fig. 7.1 (**a**) T1W sagittal image: Bony destruction at thoracic T10 and T11 vertebrae due to Pott's disease, paravertebral extension of soft tissue component composed of granulation tissue, an abscess is seen between T10-T11 vertebral bodies with intraosseous component, destructing end plates. There is also spinal canal narrowing and significant cord compression due to bulging of posterior margin of destructed T11 body. (**b**) T1W sagittal image (post-contrast): Contrast enhancement of destructive lesions of Pott's disease is seen at thoracic T10 and T11 vertebrae. (**c**) T2W sagittal image: Typical bony destruction at thoracic T10 and T11 vertebrae, paravertebral extension of soft tissue component, an abscess is seen between T10-T11 vertebral bodies, destructing end plates. There is also spinal canal narrowing and cord compression due to bulging of posterior margin of destructed T11 body (compressive myelopathy)

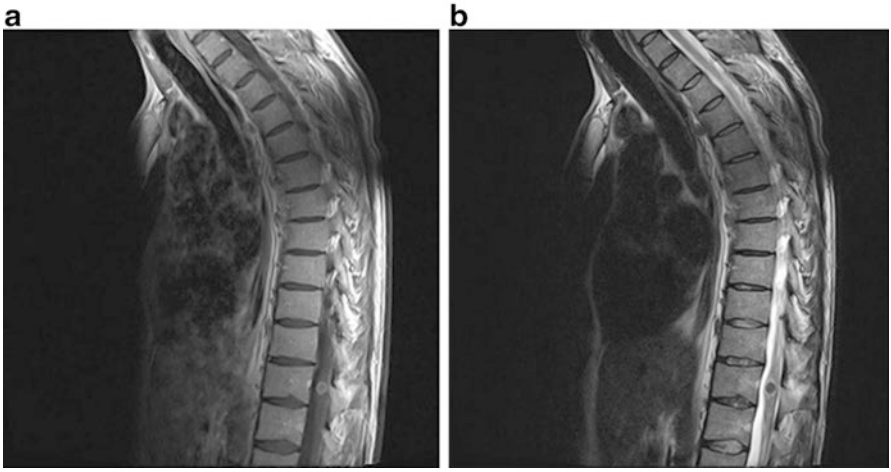

Fig. 7.2 (**a**) T1W sagittal image (post-contrast)**.** Height of the vertebral bodies decreased in multiple levels and intervertebral joint spaces narrowed due to Pott's disease. A spinal tuberculoma can be seen in the distal spinal cord at the level of thoracic T11 vertebra. It shows contrast enhancement peripherally in post-contrast series image. (**b**) T2W sagittal image: The spinal tuberculoma at the level of thoracic T11 vertebra is seen as hypointense centrally and hyperintense peripherally

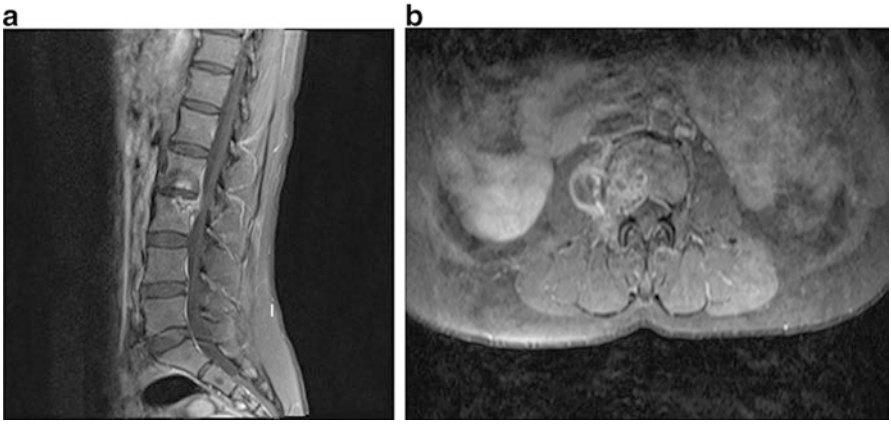

Fig. 7.3 (**a**) T1W sagittal image: Involvement of end plates and bodies of lumbar L2 and L3 vertebrae and L2 and L3 intervertebral disc due to Pott's disease. (**b**) T1W axial post-contrast image: A psoas abscess with contrast enhancement peripherally which developed secondary to Pott's disease of lumbar vertebrae at the right paravertebral area can be seen

examination includes microscopy of acid-fast bacillus (AFB) stained specimen and mycobacterial culture. Microbiologic diagnosis can be established in ¾ of the patients if appropriate specimens can be obtained [12]. If the mycobacteria can be isolated in TB culture, drug susceptibility testing is essential to prescribe optimal therapeutic regimen [57–59]. Culture of the material from draining sinuses may show colonizing microorganisms. Deep bone or soft tissue material is necessary for the correct diagnosis of causative pathogen. If CT- or US-guided FNAB reveals caseating granulomas and AFB, the diagnosis of ST is confirmed. Other granulomatous diseases such as brucellosis, fungal infection, infection with nontuberculous mycobacteria should be considered in the differential diagnosis of ST. Although currently not FDA-approved for use in extrapulmonary TB, molecular diagnostic methods such as nucleic acid amplification can be used to improve the diagnostic probability. They have promising results in diagnosis of musculoskeletal TB, but they lack sensitivity despite having high specificity [59–61]. Furthermore, in TB highly endemic countries, availability of the rapid automated growth systems and molecular tests such as Xpert MTB/RIF assay to detect nucleic acids and rifampin resistance may be limited [60]. The sensitivity and specificity of Xpert MTB/Rif assay are 62% and 100%, respectively [62].

In resource-limited countries with high TB endemicity, the diagnosis of ST is usually based on epidemiological, clinical, and radiological features. Erythrocyte sedimentation rate (ESR) is usually elevated in more than 80% of the patients as in other forms of osteomyelitis [63].

7.5 Differential Diagnosis

The differential diagnosis of ST includes other subacute or chronic granulomatous and non-granulomatous infections of the vertebrae caused by *Brucella* spp., *Candida* spp., other endemic fungi, *Actinomyces* spp., *Burkholderia pseudomallei* (melioidosis), and some bacteria such as *Staphylococcus aureus* [64]. Epidemiological features should be considered in the differential diagnosis of infectious etiology. In comparison to brucellar spondylodiscitis, ST presents with suppurative abscess formation requiring surgical drainage and spinal complications more commonly [65]. Noninfectious diseases such as spondyloarthropathy, degenerative processes, osteoporotic collapse of vertebral bodies, traumatic fractures, and especially primary or metastatic malignancy may mimic ST [7, 66].

7.6 Treatment

The main objectives of treatment are immediate relief of the symptoms (pain, paraparesis, and paraplegia), restoration of neurological and motor function, prevention of development of permanent long-term sequelae, and eradication of the infection.

Early diagnosis and prompt treatment with appropriate anti-TB drug regimen can prevent the development of sequelae such as neurologic deficit and spinal deformity. The principles of pulmonary TB treatment either for drug-susceptible or drug-resistant Mycobacteria are also valid for extrapulmonary TB forms [67]. Modern management strategies of ST have been defined by the British Medical Research Council group which organized randomized trials in patients with ST [68]. A large number of patients were enrolled in those trials, but patients with cervical ST were not included because of its low incidence. Treatment recommendations for patients with cervical ST are mostly based on case series studies [69–71]. Rifampin-based anti-TB treatment for longer courses plus anterior approach surgery when indicated resulted in full recovery in most of the patients with cervical ST. A laminectomy is not as effective in relieving cervical spinal cord compression. Moreover, because of the risk of instability of the cervical spine, it is not recommended [69]. Also, patients with myelopathy were excluded. However, in another study, medical treatment was sufficient for functional or complete resolution of myelopathy [72].

Antituberculous Therapy Medical therapy with anti-TB drugs only is sufficient in most of the patients without any neurological deficit. Standard anti-TB drug combination of isoniazid, rifampin, and pyrazinamide, with or without ethambutol given for 6, 9, or 12 months plus surgery when indicated, constitutes the mainstay of treatment of ST. Selection of the antituberculous (anti-TB) drug regimen differs whether or not the Mycobacteria are drug-resistant and whether the patient is HIV-infected or not. The optimum duration of antimicrobial therapy is uncertain and depends on the susceptibility of isolated Mycobacteria and the composition of the anti-TB drug regimen. Longer treatment duration (12–18 months) has been recommended previously for ST. However, it has been shown that 6–9 months of therapy with rifampin-based first-line anti-TB drugs (i.e., isoniazid plus rifampin for 6 months and streptomycin for the first 3 months) combined with surgical excision and bone grafting is sufficient in patients with susceptible mycobacteria and good response to therapy [7, 73, 74]. Six-month, 9-month, and 18-month regimens after radical surgical debridement gave out similar results. No recurrence or reactivation of TB was observed in patients receiving any of the three regimens [73]. In selected patients who underwent surgical intervention including thorough debridement, bone grafting, and internal fixation, even an ultra-short-course therapy of 4.5 months was as successful as a 9-month therapy [75]. In contrast, a retrospective study reported a high rate (62%) of relapse with a 6-month of therapy, while no relapse was observed with 9 month course of treatment [74]. Nine to 12 months of therapy are necessary in advanced cases with poor therapeutic response, multidrug-resistant tuberculosis (MDR-TB) [67, 76]. Osteoarticular multidrug-resistant tuberculosis (MDR-TB) has rarely been reported in the medical literature. A favorable clinical outcome can be achieved with second-line antituberculous drugs and surgery when indicated in those cases [77].

Immobilization by bed rest and/or body casts/orthosis is recommended for patients with ST of thoracolumbar junction and more than 50% loss in vertebral height and those who have severe pain. Konstam and Blesovsky reported an ambulatory treatment without immobilization or bracing and medical therapy with at

least 12 months course of isoniazid and p-aminosalicylic acid (PAS) for ST [78]. Surgery was performed in only a small percentage of patients who needed abscess drainage. Eighty-six percent of patients recovered completely with chemotherapy alone.

CDC, Infectious Diseases Society of America (IDSA), and American Thoracic Society (ATS) guidelines for treatment of spinal TB recommend medical rather than surgical treatment in uncomplicated cases [67], because surgical debridement in combination with medical treatment did not provide any additional benefit compared to medical treatment alone in uncomplicated cases [72, 79]. In a systematic review and meta-analysis, medical management of spinal epidural abscess failed in nearly 30% of the cases and required surgery [80].

Surgical Therapy There is heterogeneity in the percentage of patients who required surgery [12]. In approximately 2/3–3/4 of the patients, surgery may be necessary [26, 81]. Medical treatment alone was implemented in 1/3 of the patients, while diagnostic and/or therapeutic surgical intervention was required in the remaining 2/3 [27].

The indications for surgery include kyphosis >40 degrees at presentation (kyphotic angle is measured from lateral spinal X-ray using the modified Konstam method) or progressive kyphosis, neurologic deficits due to spinal cord compression in advanced cases, progression of neurological deficits despite appropriate therapy (ongoing deterioration)/poor response to chemotherapy, drainage of cold abscesses, spinal instability, and diagnostic purposes in patients with nondiagnostic FNAB results. Surgery should be performed early in patients with acute neurological impairment and instability of the spinal column. It may be delayed in clinically and neurologically stable patients [67, 68, 82–85].

The purposes of surgical therapy are debridement and removal of infected tissues, relief of pain, and improvement of neurological deficits by decompression and spinal stabilization, correcting any deformities and restoring function [1]. Surgical therapy includes debridement of infected material, drainage of abscesses if present, decompression, bone grafting, and spinal stabilization by hardware use [85, 86]. Depending the portion of the vertebral body and the vertebral level involved, whether cold abscesses are present or not, different surgical approaches have been described [87–89]. In early phase of the disease, posterior stabilization with hardware instrumentation is performed to prevent kyphosis. Anterior surgical approach is preferred in some cases who present with spinal deformity late in the course of the disease to prevent progression of the deformity [68]. Hodgson et al. reported a success rate with anterior approach surgical decompression by resection and autologous bone grafting and anti-TB chemotherapy [90]. Reconstructive surgery for correction of spinal deformities (e.g., kyphosis) may be needed in some cases after completion of anti-TB therapy. Hardware use may be required for stabilization of the vertebral column [89]. Patients with neurological symptoms and/or destructive bone lesions of the thoracic or lumbar vertebrae may benefit from minimally invasive surgical interventions such as video-assisted thoracoscopic anterior surgery [91, 92]. The need for surgery in treatment of musculoskeletal tuberculosis involving

other parts of the skeleton is not always clear [79]. Therefore, surgery is not warranted routinely in all cases of ST [93, 94].

Neurological motor deficit has been graded in four categories as Grade1, negligible; Grade 2, mild; Grade 3, moderate; and Grade 4, severe (including sensory and autonomic dysfunctions). Conservative treatment is recommended in Grade 1 and 2; surgical therapy is favored in Grade 4. Grade 3 patients remain in gray zone in which there is no consensus on decision of therapeutic modality [95].

Management of ST in HIV-negative and HIV-infected patients does not differ [95]. But monitorization for immune reconstitution inflammatory syndrome (IRIS) is highly recommended in HIV-infected patients receiving concomitant anti-TB therapy for ST and antiretroviral treatment (ART) for HIV infection. After initiation of ART, paradoxical progression of clinical and laboratory findings of TB should alarm for the development of IRIS. IRIS presents with new clinical manifestations and/or imaging findings, or reappearance of resolved signs or symptoms [96, 97].

For surgical treatment of thoracic and lumbar ST, either anterior or posterior approach surgery may be preferred, but posterolateral approach allows better correction of the kyphotic angle and improvement in back pain [98]. However, posterolateral surgery takes more operative time and causes more blood loss and postoperative sinus formation [99–101]. Furthermore, patients who have not improved after posterior approach surgery may need anterior approach surgery [88]. For the treatment of thoracic and thoracolumbar ST, single-stage transpedicular debridement, posterior instrumentation, and fusion have been reported to be effective with satisfactory long-term postoperative outcomes [102]. In patients with single-segment spinal tuberculosis, use of titanium mesh cages resulted in comparable clinical efficacy with autologous iliac bone grafts. They can also be used in surgical treatment of multi-segment spinal tuberculosis with good clinical efficacy [103]. In thoracic ST with multilevel contiguous vertebral involvement, posterior instrumentation was more useful for durable correction of kyphosis [99]. Also, posterior surgical approach is effective in treatment of lumbosacral spinal TB [104, 105].

Monitorization of Response to Therapy Clinical response is assessed by resolution of the symptoms and signs and improvement of sensory and motor neurological functions. Inflammatory markers such as C-reactive protein (CRP), ESR have a limited role in evaluation of response to therapy. A two-third reduction in serial ESR measurements and decrease in CRP levels within 6 weeks in the postoperative period may indicate good response to therapy and rapid neurological recovery [106]. Despite appropriate therapy, radiological findings may resolve lately in the course of disease, even progression may be observed. Thus, repeated serial imaging studies are not recommended [107]. Mild weakness/improved muscle power, lower paraplegia scores, sensory-evoked potentials (SEPs), and motor-evoked potentials (MEPs) were the predictors of 6-month favorable outcome in patients with paraplegia due to Pott's disease [108]. Follow-up of the patients should continue until at least 1–5 years year after completion of treatment to determine long-term outcome of therapy.

7.7 Prognosis

Favorable outcome in ST can be defined as "full physical activity of the skeleton with clinical and radiological improvement of the disease, with no functional impairment." Levels of vertebral involvement, the score of the patient according to American Spinal Injury Association Impairment Scale (AIS grade) at presentation, and bladder and bowel involvement affect the final outcome of neurological improvement significantly [35].

Two percent mortality has been reported by Turgut M et al. and by Batirel A et al. in their study including a total of 694 cases and 314 cases with ST, respectively [27, 31]. Permanent sequelae have been reported in ¼ of the patients due to delayed diagnosis. The most common sequelae (4–11%) were kyphosis/gibbus deformity, scoliosis, paraparesis, paraplegia, and loss of sensation [27]. Older age, presence of spinal deformity, and neurologic deficit were found to be predictors of unfavorable outcome [27].

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Chapter 8
Tuberculous Meningitis

Derya Ozturk-Engin and Corneliu Petru Popescu

8.1 Introduction

Tuberculous meningitis (TBM) is an important public health problem caused by *Mycobacterium tuberculosis*. Central nervous system (CNS) tuberculosis accounts for 1% of all tuberculosis cases and for 5–10% of extrapulmonary tuberculosis cases [11]. The most devastating form of tuberculosis is TBM [7]. Approximately half of patients with TBM receiving antituberculosis treatment develop severe sequelae or mortality [106]. Neurological sequelae of TBM include cranial nerve palsy, hemiparesia/focal weakness, cognitive impairment, motor deficits, vision impairment, stroke, seizure, hearing impairment, and altered consciousness [12, 47, 53, 69].

That the clinical presentation of TBM is non-specific and that the sensitivity of laboratory tests used for diagnosis is low or takes a long time leads to delay in diagnosis. Delay in diagnosis and treatment has an adverse effect on the prognosis [7, 41].

8.2 History

The genus *Mycobacterium* is thought to have emerged millions of years ago [21]. As to the historical identification and introduction of TBM, Robert Whytt was the first to give an account of the clinical signs and symptoms in a report published in

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1768 [8]. TB meningitis was first defined as distinct pathological entity and coined the term "tubercular meningitis" in 1836. This definition was the result of his work to correlate clinical findings with pathological observations of children who died from acute hydrocephalus. Pointing out the similarity to tubercular peritonitis characterized by tubercles, he concluded that hydrocephalus was associated with granulations and tubercular infiltration [109].

Next to be acknowledged is Robert Koch for the identification and isolation of the causative agent of tuberculosis in 1882 [89]. James Leonard Corning was the first to perform the examination of the spinal fluid in 1885, and the discovery of lumbar puncture is credited to Heinrich Quincke, who also applied it for diagnostic purposes and introduced it for clinical practice in 1891 [14, 113]. Performing a series of postmortem examinations, Rich and McCordock documented areas of caseation in the brain parenchyma and meninges virtually in the majority cases of TBM. The rupture of these caseating focus allowed dissemination of the bacilli for the bacilli to enter the subarachnoid space, causing meningitis [4, 86].

8.3 Epidemiology

Approximately one-third of the world's population is thought to have latent tuberculosis [52]. Tuberculosis is the ninth cause of death in worldwide. In 2016, there were 10.4 million tuberculosis cases. Of note, HIV-infected individuals account for 10% of all tuberculosis cases. Only five countries account for 56% of the total tuberculosis population, including India, Indonesia, China, the Philippines, and Pakistan [77]. In 2014, 9.412 new tuberculosis cases were reported in the United States. The total number of cases, the rate of foreign-born individuals, was 13.4 times higher than the rate among US-born individuals [94]. For 2013 alone, a total of 13,409 cases were notified from Turkey, including 4731 extrapulmonary tuberculosis [49] (http://tuberkuloz.thsk.saglik.gov.tr/Dosya/Dokumanlar/raporlar/).

In countries with a high prevalence of tuberculosis, CNS tuberculosis usually afflicts very young children (<3 years of age), while in countries with a low prevalence, the majority of patients are immigrant adults who have migrated from countries with a high prevalence [103].

HIV-infected individuals are at increased risk for tuberculous meningitis [119]. In addition to HIV infection, other risk factors for tuberculosis have been reported as diabetes, malnutrition, alcoholism, malignancies, and the use of immunosuppressive agents [59, 86]. Close contact to an individual with active tuberculosis or prior tuberculous history are detected about 75% of patients with TBM [56].

The protection of the BCG vaccine against tuberculosis is controversial [102]. Its protection against pulmonary tuberculosis has been reported to be suboptimal; it was found protective against miliary or meningeal tuberculosis at a rate of 86% in randomized controlled trials and at a rate of 75% in case-control studies [66, 87].

According to the findings of a meta-analysis, the BCG vaccine confers 50% protection against tuberculosis [20]. Other meta-analysis showed that BCG vaccination protect against tuberculosis for up to 10 years [1].

8.4 Etiology and Pathogenesis

M. tuberculosis is a gram-positive bacterium weakly stained due to its thick cell wall containing lipids, peptidoglycans, and arabinomannans. The bacillus associated with only humans is obligate aerobic, nonspore-forming, and acid-fast bacillus (AFB). Standard staining techniques using Ziehl-Neelsen, Kinyoun, or auramine-rhodamine dyes allow the detection of nearly 100 AFB/ml of the cerebrospinal fluid (CSF) [86]. Compared with other bacteria whose division times correspond to minutes, division of *M. tuberculosis* is extremely slow, being every 15–20 h.

Carried in airborne particles, *M. tuberculosis* enters the host through inhalation. The bacillus reaches the macrophage within the alveoli and replicate (Fig. 8.1) [4]. The primary complex occurs with the spread of the localized infection within the lungs to the regional lymph nodes. At this stage, a short but significant bacteremia occurs, allowing the tubercle bacilli to seed to the other organs in the body, including the meninges or brain parenchyma [7].

During bacillemia that follows primary infection or disseminated disease, metastatic caseous lesions seeded to the subependymal or subpial tubercles, also referred to as the "Rich foci," increase in size and rupture into the subarachnoid space,

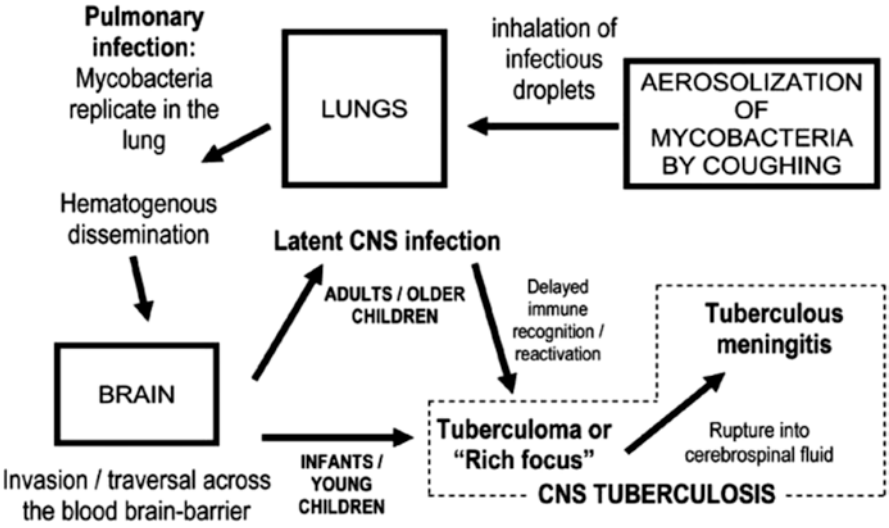

Fig. 8.1 Spread to the central nervous system of *M. tuberculosis* [4]

resulting in TBM [66]. The inflammatory reaction against and the bacilli and tuberculosis antigens released from the Rich foci results in some pathological changes in the brain [7]. A study on CSF cytokine levels of TBM patients found significantly elevated levels of TNF-α, sTNFR-75, sTNFR-55, IFN-γ, and IL-10 [67]. Obstruction of the CSF by inflammatory infiltrate leads to hydrocephalus. Vasculitis contributes to the occurrence of infarction, which in turn gives rise to neurological damage [4].

Among individuals infected with *M. tuberculosis*, active disease usually develops in 10% 1–2 years after exposure [26]. Despite exposure, it still remains unclear why the disease does not develop in some individuals. Some investigators think this may have multifactorial causes [102]. The outcome of exposure to *M. tuberculosis* may be based on both the pathogen lineage (Beijing genotype), and an effect on the human gene function includes interferon gamma, solute carrier family 11, member 1 (SLC11A1), TIRAP/MAL, P2XA7, CCL2, SNP T597C TLR2, and LTA4H [7, 15].

8.5 Pathology

Apart from the meninges, TBM also affects the parenchyma and vasculature of the brain. The histopathologic features of TBM present as a thick basal exudate consisting of lymphocytes, mononuclear cells, epithelioid histiocytes, and areas of necrosis with granuloma formation. Autopsy studies have documented basal exudates in almost all cases (96%) [17]. Exudate formation may obstruct CSF flow resulting in hydrocephalus; granulomas may combine to form abscesses or tuberculomas causing focal neurological deficits, and obliterative vasculitis may give rise to infarcts and stroke [109]. The caseous necrotic center of tuberculomas is surrounded by a capsule containing lymphocytes, Langhans giant cells, epithelioid cells, and fibroblasts [90].

The spectrum of vascular involvement in TBM includes arteritis, arterial spasm, arterial thrombosis, and compression of larger arteries by a thick exudate [17]. Arteritis often affects the branches of the major arteries at the base of the brain [72]. While necrotizing lesions are observed in acute fulminant cases, proliferative lesions are more common in subacute cases [17].

8.6 Clinical Presentation

The clinical spectrum is broad, TBM may have from chronic headache or mild mental status changes to symptoms and signs of usual meningitis, most frequent headache, fever, neck stiffness, vomiting, and sometimes sudden, severe meningitis progressing to coma. A prodromal phase is present with malaise, intermittent headache, low-grade fever, and weight loss, 3–4 weeks before acute onset, usually

without neck stiffness [64, 99]. In different studies fever may be absent; it is present from 19% to 99% of patients [3, 58].

After the prodromal phase, with the installation of the meningitis symptom, clinical manifestations of the disease may include hemiparesis, confusion, seizures, cranial nerve palsies, movement disorders, diplopia, stupor, movement disorders, and coma [3]. Sometimes, focal neurological signs are acutely installed without the prodromal phase [64].

Clinical presentations are different depending on the age of the patients: children have in the prodromal phase cough, fever, vomiting (without diarrhea), malaise, and weight faltering over adults who may have malaise, weight loss, low-grade fever, and gradual onset of headache over 1–2 weeks, followed by worsening headache, vomiting, and confusion, leading to coma and death if untreated [107, 108]. Headache occurs less often in children than in adults [86]. Children also have more frequent initial apathy or irritability, decreased level of consciousness, and signs of raised intracranial pressure (often bulging anterior fontanelle and abducens nerve palsy). On the other hand, adults have more cranial nerve palsies (VI > III > IV > VII) developing as disease progresses and confusion and coma deepen: monoplegia, hemiplegia, or paraplegia [108].

The British Medical Research Council (BMC) established in 1948 severity grade for TBM which was completed in 1974 with the introduction of Glasgow Coma Scale (GCS). Stage 1 (early) corresponds to alert and oriented patient without focal neurological deficits with GCS score of 15. Stage 2 (medium) firstly corresponds to patient's condition that falls between early and advanced but after 1974 is defined as a Glasgow Coma Scale of 11 to 14 or 15 with focal neurological deficits. Stage 3 (advanced) corresponds to patient being extremely ill and in a deep coma and, after 1974, is defined as a GCS of 10 or less with or without focal neurological deficits [86, 123].

Clinical manifestations of concomitant extrameningeal tuberculosis may appear, especially pulmonary disease; in other cases there are no clinical or historical manifestations to suggest tuberculous etiology [37, 58]. In infants, before TBM, firstly occurs primary pulmonary infection [108]. TBM in children develops most often within 3 months of primary tuberculosis infection [29].

Influence of the immun response against *M. tuberculosis* occurs young patients (less 1 year of age) or HIV coinfection [107, 115]. In these patients extrapulmonary dissemination are more easily and TBM can be installed abrupt with rapid evolution to coma and prostration and associated with high mortality [123].

In HIV coinfected patients if compare TBM with cryptococcal meningitis was observed that neck stiffness, higher body temperature and reduced consciousness are more frequent in TBM [19]. TBM can lead to severe complications: hydrocephalus (80% of TBM patients have communicating hydrocephalus), tuberculomas, ventriculitis, vasculitis, and cerebral ischemia, all contributing to high mortality and severe sequelae in patients with TBM. In case of complications, neurological manifestations of TBM may persist or worsen [123].

8.7 Diagnostic Tests

Routine laboratory tests fail to yield differential results in TBM cases. Patients may have leukopenia, leukocytosis, or a normal leukocyte count [47, 81]. Tuberculous meningitis may also be associated with metabolic complications. Most commonly detected is hyponatremia, which affects 45–79% of patients [23, 70]. Hyponatremia may result from cerebral salt-wasting syndrome, the syndrome of inappropriate antidiuretic hormone secretion, excessive fluid intake due to impaired sense of thirst, or use of mannitol or treatment of diabetes insipidus [50].

8.8 CSF Analysis

The diagnosis of TBM depends on CSF analysis following a lumbar puncture. On CSF examination, the appearance is clear or slightly opalescent. An initial CSF pressure above 25 cm H_2O is determined in 50% of cases [109]. When kept at room temperature or in the refrigerator, a "cobweb"-like appearance is formed on the surface of the CSF [56]. There is moderate pleocytosis in the CSF of the patients with TBM (Table 8.1). The cell count is 100–500 cells/μl, with a predominance of lymphocytes, though there may be an early predominance of polymorphonuclear leukocytes in the first 10 days of disease [102]. Acellular CSF has also been reported in elderly and HIV-infected individuals [16, 54]. A CSF protein level between 100 and 500 mg/dl and a glucose level below 45 mg/dL or a CSF/plasma ratio of less than 0.5 are typical of TBM [66]. However, there have been cases reported to have a CSF protein level above 5 g/l and a normal glucose level [117].

The detection of acid-fast bacilli in the CSF by the Erlich-Ziehl-Neelsen staining is a cheap and rapid test. Its sensitivity varies between 10 and 60% depending on the laboratory and the experience of the technician [33]. Increasing the duration of the microscopic examination, examination of the CSF specimen in large volumes (10 ml), and repeated lumbar punctures are said to increase the sensitivity of the test [7, 102].

For diagnosis, the identification of *M. tuberculosis* in the CSF by direct culture is the gold standard. Smear microscopy and culture method requires 10^4–10^6 and 10^1–10^2

Table 8.1 The CSF findings in the patients with tuberculous meningitis

Reference no	No of patients	CSF glucose (mmol/L)	CSF protein (mg/dl)	CSF WBC (/mm^3)
Verdon et al. [117][a]	47	1.9 ± 1.3	345 ± 286	273 ± 722
Roca et al. [85][b]	29	1.33(0.94–1.77)	125 (98–246)	148 (65–388)
Hsu et al. [48][a]	46	2.35 ± 1.90	346.3 ± 548.1	221.8 ± 306.5
He et al. [44][a]	161	2.11 ± 1.53	138.7 ± 70.4	198 ± 198

[a]Mean ± standard deviation
[b]Median (min-max)

bacilli/mL of sample respectively, are required [6]. Culture positivity on the Lowenstein-Jensen (L-J) medium ranges between 25% and 75% [7]. To ensure maximum sensitivity, incubation requires up to 8 weeks, and a large amount of labor is needed. In contrast, incubation in the radiometric liquid culture medium shortens the duration significantly, providing a positive result within a mean of 13 days [51]. However, it is crucial to start treatment as early as possible while awaiting culture results. In a study of 256 cases of *M. tuberculosis*, isolation rates were 93% and 39% with the radiometric liquid culture medium and the L-J medium, respectively [116]. In another study, the sensitivity rates for the automated culture and L-J systems were 81.8% and 72.7%, respectively. Combined use of the L-J and automated systems has been reported to be superior to using either of the tests alone [33].

The low sensitivity of the acid-fast bacilli smears and prolonged time for obtaining culture results have sparked the search for new diagnostic methods. The ELISA test is used to detect antibodies against specific mycobacterial antigens in the CSF. In a study in which indirect ELISA was used, the humoral immune response (both IgG and IgA) against 16-kDa antigen was determined in patients with TBM, with a sensitivity of 42.8% and specificity of 94.7% [57].

8.9 Chest X-Ray

A chest X-ray may show findings compatible with active pulmonary disease in 30–65% of adults with CNS tuberculosis [83, 85, 100]. In children with TBM, radiographic findings of tuberculosis are more likely to be seen in HIV-infected than in non-HIV-infected subjects (84% *vs.* 70%). Compared with non-HIV-infected patients, hilar lymphadenopathy, pleural effusion, and cavity formation have been reported to be more frequent in HIV-infected patients [100].

In a study conducted in children with TBM, abnormal findings on chest radiography were found in 43%, which included hilar adenopathy in 32%, miliary pattern in 18%, and bronchopneumonic infiltrate in 24%. In the same study, chest computed tomography was found to be superior to chest X-ray examination, detecting abnormal findings in 88% of children (mediastinal and hilar lymphadenopathy in 46%, bronchopneumonic infiltrate in 23%, and miliary pattern in 23%). The authors concluded that chest computed tomography was helpful in detecting abnormalities that might go unnoticed on conventional X-rays [124].

8.10 Radiology

Computer tomography (CT) and magnetic resonance imaging (MRI) have improved the diagnostic accuracy of TBM. Neuroimaging can be helpful in the early diagnosis [46]. Unfortunately, 30% of patients have normal brain CT scans, and around 15% have normal brain MRI scans in the early stage of TBM [2, 123].

The most frequent identified neuroradiological features of TBM include basal meningeal enhancement, hydrocephalus, and infarctions in the supratentorial brain parenchyma and brain stem [5].

Tuberculous meningitis appears due to hematogenous spread, rupture of a Rich focus, or direct extension from CSF infection [22] with thick gelatinous exudate in the basal cisterns early detected by CT or MRI. Initially, in early stages of the disease, noncontrast MRI studies usually show little or no evidence of any meningeal abnormality, but with disease progression, swelling of the affected subarachnoid spaces occurs with associated mild shortening of T1 and T2 relaxation times in comparison with normal CSF [111]. Some degree of involvement of the meninges within the sulci over the cerebral convexities and in the Sylvian fissures is also seen in most cases. These findings are better seen at gadolinium-enhanced MR imaging than at CT [10]. Basal meningeal exudates, identified by contrast-enhanced CT imaging, were specific for TBM and predicted poor outcome [9]. The meninges appear hyperintense on pre-contrast T1-weighted magnetization transfer (MT) images and enhance further on post-contrast T1-weighted MT images. The MT ratio in TBM is significantly higher than in viral meningitis but smaller compared with fungal or pyogenic meningitis [39, 43].

Severe visual loss appears when TBM manifests as optochiasmatic arachnoiditis. Thick basal exudates are dominantly present in the interpeduncular, suprasellar, and Sylvian cisterns with “spider leg appearance” on the CT scan [40].

Age and HIV coinfection influence radiological features; thus, children with TBM are more likely to exhibit hydrocephalus than are adults with TBM. Basal enhancement is often less prominent in people coinfected with HIV-1 due to an impaired immunological response resulting in the absence of basal meningeal exudates [24, 55, 123].

Evolution of meningeal enhancement may be to develop an initial increase despite adequate antituberculous therapy, healing with the absence of basal meningovascular enhancement, or even persist in some cases of TBM [5]. The exudate extension leads to infarctions and/or hemorrhage, especially in the basal ganglia and internal capsule regions, that is earlier detected with MRI [71].

Viewing complications of TBM on radiology is very important to establish long-term outcomes and evolution under treatment. Thus, detection and localization of ischemia and infarcts by MRI added new data about evolution of TBM [76, 114]. Visualization of small leptomeningeal tuberculomas (which are present in about 90% of children and 70% of adults with the disease) [108] and the detection of small areas of ischemia or early infarction are more feasible with MRI than CT scan [123].

A rare aspect of TBM may be the intracranial aneurysm formations [61, 71]. Tubercular ventriculitis is also a rare complication of TBM observed by MRI with intraventricular septations, sequestration of ventricles, and hyperintense ependymal wall of the affected ventricles on magnetization transfer images on MRI [98].

8.11 Tuberculin Skin Test

The tuberculin skin test (TST) is performed to determine whether a person is infected with *M. tuberculosis*. A delayed-type hypersensitivity reaction becomes detectable 2–8 weeks after infection. A 0.1 ml of 5 TU purified protein derivative solution is injected intradermally into the forearm, and the ensuing reaction, i.e., the transverse diameter of the palpable induration, is read and interpreted within 48–72 h of administration. A 5 mm or greater induration is considered to be a positive result in immunosuppressed subjects, including HIV-infected persons, those having close contact with tuberculosis cases, those having clinical or radiological evidence of current or prior tuberculosis, and individuals receiving tumor necrosis factor inhibitors. A 10 mm or greater reaction is considered to be positive for individuals who are at a high risk for latent tuberculosis, such as those born in countries with a high incidence of, or exposed to occupational risks of, tuberculosis. For all other persons, skin test may be considered to be positive if the reading is 15 mm or greater [63].

The skin test may yield a false-positive result in the presence of an infection with nontuberculous mycobacteria, incorrect administration of the test, a previous BCG vaccination, incorrect reading and interpretation, and even the use of an incorrect bottle of antigen. Similarly, false-negative results may be associated with cutaneous anergy, very old (many years) or very recent (within 8–10 weeks of exposure) tuberculosis infection, very young age (<6 months), some viral illness, recent live-virus vaccination (e.g., for measles or smallpox), overwhelming tuberculosis, or incorrect administration, reading, or interpretation of the test [75].

The skin test is interpreted as positive in 10–50% of cases with CNS tuberculosis; these rates vary between 30% and 65% in children [103].

8.12 Interferon-Gamma Release Assays (IGRAs)

Interferon-gamma release assays (IGRAs) are blood tests that can be used to diagnose *M. tuberculosis* infections. However, they do not differentiate latent infection and tuberculosis disease. QuantiFERON® -TB Gold-in-Tube test (QFT-GIT) and T-SPOT®.TB test (T-spot test) are the two FDA-approved IGRA tests [63]. The former measures the concentration of interferon-gamma (IFN-g) released by white blood cells when confronted with tuberculosis-specific antigens such as ESAT-6, CFP-10, and TB7.7, while the latter measures the number of IFN-g-producing cells activated by ESAT-6 and CFP-10 [13, 62]. The sensitivity of measuring the IFN-g concentration was reported to be 90.2% [33]. As for measuring the number of IFN-g-producing cells, the specificity and sensitivity rates were found as 92.8% and 83.6%, respectively [25].The skin test and IGRAs have been compared in several studies. Some reported similar sensitivity rates, while some reported higher sensitivity rates for the T-spot test, when compared with the skin test, particularly in the presence of immunosuppression or miliary tuberculosis [60, 68].

8.13 Tuberculostearic Acid

Tuberculostearic acid (TSA) is a structural component of *M. tuberculosis*. It is detected in the CSF using gas chromatography/mass spectrometry with selected ion monitoring [38]. Positive results were reported in five of six culture-positive patients and none in 19 culture-negative patients with diagnoses of bacterial or viral meningitis. This method yielded positive results in four of ten patients whose other confirmatory laboratory tests were negative for suspected TBM [31].

8.14 Adenosine Deaminase

Adenosine deaminase (ADA) is an enzyme involved in the catabolism of purine and plays a significant role in the maturation of monocytes, macrophages, and T lymphocytes. Its activity is elevated in lymphoid tissues, especially in active T lymphocytes, which makes it an important marker for diseases associated with T-cell-mediated immune response. This test may be used in the confirmation of TBM, but its activity also increases in other CNS disorders such as sarcoidosis, lymphoma with meningeal involvement, subarachnoid hemorrhage, and neurobrucellosis [56].

In a meta-analysis of 13 studies involving 380 patients with TBM, the value of the ADA test was assessed in the diagnosis of TBM: levels of 1–4 U/l were found to be helpful to exclude the diagnosis (sensitivity >93%, specificity <80%); levels between 4 and 8 U/l were found to be insufficient to confirm or exclude the diagnosis; and levels above 8 U/l were found to improve the diagnosis (sensitivity <59%, specificity >96%) [112]. Having a supportive role in the diagnosis, the CSF ADA activity is not recommended as a routine diagnostic test in TBM [44].

8.15 PCR

The prolonged incubation period in culture and an increased need for non-culture diagnostic methods have paved the way for molecular-based methods for the detection of *M. tuberculosis* in the CSF. Nucleic acid amplification testing (NAAT) allows identification of *M. tuberculosis* in clinical specimens or culture. With this method, it is even possible to detect fewer than ten bacteria [109]. After the initiation of treatment, mycobacterial DNA can be detected in the CSF for up to 4 weeks [30]. In a meta-analysis of 14 studies evaluating the value of NAAT in TBM, this amplification test showed a sensitivity of 56% and specificity of 98% [79]. Sensitivity is high for smear-positive respiratory samples and low for smear-negative non-respiratory samples. A negative result does not exclude the diagnosis of tuberculosis [109]. Most PCR-based studies may yield false-negative results due to the use of a

single target gene for amplification and the absence of the target gene in some isolates of *M. tuberculosis* [66].

The polymerase chain reaction (PCR) is the most common method, but there are also alternative amplification methods like real-time PCR, isothermal strain displacement amplification, transcription-mediated amplification, and ligase chain reaction. The World Health Organization (WHO) recommends the use of line probe assays (LPAs) and the Xpert MTB/RIF test for the detection of *M. tuberculosis* [109].

8.16 Treatment

In TBM, treatment is an emergency. Antituberculosis treatment should be initiated immediately, on the basis of strong clinical suspicion [73, 120]. It should not be delayed till the bacteriologic proof is obtained. Mostly the mortality and morbidity depend on the stage of therapy initiation. The balance benefit/risk is superior, and greater harm can be installed with a delay of antituberculous therapy (even only a few days) than with inappropriate treatment meanwhile searching for the right diagnosis. Antituberculosis treatment includes two essential arms, chemotherapy and glucocorticoids.

The treatment of drug-susceptible TBM follows the regimens used against pulmonary tuberculosis even if these recommendations do not take into account that antituberculosis drugs have difficulties to penetrate the brain barriers and the concentration in the CSF is under 10–30% of plasma levels [28, 32, 45, 74]. Ethambutol is less effective in meningeal disease and even into inflamed meninges has a poor penetration [27]. The WHO recommends 2 months of rifampicin, isoniazid, pyrazinamide, and ethambutol followed by 10 months of rifampicin and isoniazid, for all patients, but in 2003 suggested that ethambutol should be changed with streptomycin [78]. However, both drugs (ethambutol and streptomycin) seem to be correlated with a deterioration of patients even if we started the treatment in the early stages of the disease [27].

In the case of CNS tuberculosis, till now, there are no randomized controlled trials for the optimal drug combination or therapy duration. Treatment begins with a four-drug regimen for two months and continues with two-drug regimen (only if the sensibility of the isolate is available) till one year. The first three antimicrobial agents for TBM include isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) all of which enter CSF readily in the presence of meningeal inflammation. Rifampicin, isoniazid, and pyrazinamide are bactericidal. The biodisponibility of the oral formulation permits to achieve CSF levels that exceed the inhibitory concentration needed for sensitive strains so these drugs can be administered orally. RIF is efficient against both, rapidly dividing subpopulations of organisms and semidormant organisms. INH is more active against rapidly dividing organisms. PZA has a good CSF penetration and is the most effective on the intracellular mycobacteria. The fourth drug may be ethambutol [73], a fluoroquinolone (moxifloxacin or levofloxacin), or an injectable aminoglycoside (amikacin, capreomycin, kanamycin or streptomycin),

administered daily for 2 months as long as meningeal inflammation persist, because aminoglycoside penetration is optimized only in acute phase and its role beyond this time is not clear [27]. The fluoroquinolone (moxifloxacin or levofloxacin) exhibits good penetration in CNS [27]. Intensified treatments with higher-dose levofloxacin (20 mg/kg per day) and rifampin (15 mg/kg per day) are in debate, with studies suggested that an increase in rifampin dose [88] and the addition of a fluoroquinolone to the standard regimen [104] may improve the outcome in patients with TBM and other that has not proven a higher rate of survival [45]. In children with TBM, the American Academy of Pediatrics recommends an initial four-drug regimen INH, RIF, PZA, and ethionamide, if possible, or an aminoglycoside for the first 2 months [80]. The duration of the therapy requires case-to-case adjustment. The duration of the treatment should be extended to 18 months for the cases with tuberculoma.

The second-line drugs are fluoroquinolones (levofloxacin, moxifloxacin, gatifloxacin); injectable agents, aminoglycoside (amikacin, capreomycin, kanamycin, streptomycin); other core second-line drugs (ethionamide/prothionamide, cycloserine, linezolid, clofazimine), and association agents – not part of core regime (bedaquiline, delamanid, para-aminosalicylic acid, imipenem-cilastatin/meropenem, amoxicillin-clavulanate) [27, 73, 110]. Empiric second-line treatment should be started in a few cases: exposure to an individual with drug-resistant TB, residence in or travel to a region with high prevalence of drug-resistant tuberculosis, and treatment relapse or treatment failure.

Multidrug resistance (MDR) to rifampicin and isoniazid on TBM leads to mortality >80% [95, 105, 118]. For multidrug-resistant tuberculosis, there are no guidelines to appreciate the drug association or the duration of treatment. WHO recommends an initial regimen with at least five effective drugs (pyrazinamide and four second-line drugs) and also recommends to use an injectable agent for at least 8 months [35]. Total duration of treatment for MDR-TBM should probably be at least 18 months. Early and prompt knowledge about at least INH- and RIF-resistance would be most beneficial for designing anti-TB therapy [96]. In settings with GeneXpert MTB/RIF, available rapid switch to second-line agents decreases mortality [123].

In HIV coinfection and TBM, initiation of antiretroviral therapy early may be complicated by the immune reconstitution inflammatory syndrome (IRIS). This can present as reactivation of latent TB, as progression of active TB, or, in patients previously improving on antituberculous therapy, as clinical deterioration. That is why in ART-naive HIV patients with TBM, regardless of CD4 count, the initiation of the antiretroviral treatment should be delayed for 6–8 weeks from the beginning of antituberculous regimen [65, 73, 110]. On the other hand, antiretroviral treatment has been proven to decrease 9-month mortality in patients with HIV and TBM fewer than 40% [45].

From 60 years ago, intracerebral inflammation and use of steroid treatment have been recognized as determinant factors of TBM outcome [97]. A systematic review and meta-analysis of all relevant published trials concluded that corticosteroids increase survival in HIV-1-negative children and adults with TBM [82]. The steroid treatment is required urgently in several situations: patients with rapidly progressing

disease at or before the introduction of chemotherapy, presentation as acute encephalitis, CSF opening pressure ≥400 mm H_2O or clinical or computed tomographic signs of cerebral edema, "therapeutic paradoxical" exacerbation of clinical signs after debut of antituberculous chemotherapy, CSF protein >500 mg/dL and rising (spinal blockage), marked basilar enhancement on CT, and moderate or advancing hydrocephalus or intracerebral tuberculoma [41, 82, 93, 106]. Tuberculomas are paradoxical reactions to TBM treatment and high-dose adjunctive corticosteroids are associated for treatment, even if controlled trials are absent. Other adjuvant treatments for TBM when corticosteroids have no effect can be thalidomide [92]. Thalidomide can be used, when other adjuvant treatments for TBM has no effect such as corticosteroids.

The presence of vasculitis and hydrocephalus might be cause delayed therapeutic responses [11]. The management of TBM with hydrocephalus may require surgical decompression of the ventricular system for the effective control of the complications of raised intracranial pressure. While waiting the early response to chemotherapy, the combination of serial lumbar puncture, corticosteroid therapy, and other dehydrating agents (like acetazolamide, furosemide, and mannitol) may be enough in patients with stage 2 tuberculosis with communicating hydrocephalus [84, 91, 121]. However, in patients with stupor and coma or marked by progressive neurologic impairment despite medical treatment, the surgical procedures should not be delayed ([84, 42], GT). Surgical intervention with ventriculoperitoneal shunting (VPS) or endoscopic third ventriculostomy (ETV) should be used in case of noncommunicating hydrocephalus [36]. VPS is associated with a worse prognosis in HIV-infected patients when compared with HIV-uninfected patients [84]. It is difficult and not yet established when it is indicated to have surgical decompression by VPS compared with ETV.

8.17 Prognosis

The case fatality rate of TBM remains unacceptably high, ranging from 7% to 69% [18, 66]. There are a number of studies that show factors that affect prognosis in TBM. In a study of 507 patients with microbiologically confirmed TBM, altered consciousness, diabetes mellitus, immunosuppression, neurological deficits, hydrocephalus, and vasculitis were reported to have an unfavorable effect on the outcome. The authors developed a new severity index (HAMSI scoring) with scores from 1 to 6 and found the mortality rate to be 40.1% with the highest score [34].

Other risk factors for mortality were implicated as advanced stage or severe neurologic involvement at presentation, comatose mental status, delayed diagnosis and treatment, seizures, cranial nerve palsy, extreme of age, the combination of isoniazid and rifampicin resistance, HIV coinfection, CSF parameters such as high CSF lactate, CSF leucopenia, low CSF glucose, and positive cerebrospinal fluid culture for *M. tuberculosis* [47, 48, 66, 86, 101, 122, 123]. Positive TBM culture has been associated with poor prognosis has suggested that a rapid reduction in bacillary

burden might be beneficial, but no benefit could not be proven. These findings also indicate that more specified pharmacokinetic and pharmacodynamic studies of TBM are needed. High-quality studies in which molecular diagnostic methods are applied may provide new insights into the treatment of drug-resistant TBM [123].

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Chapter 9
Tuberculous Encephalitis

Jean Paul Stahl

9.1 Context

Tuberculosis is an infection with multiple localizations, the most frequent being the lung. From this initial infection, bacteria spread in the body via the blood, acting as a bacteremia. Infectious metastases are various, and among them, brain is potentially the most severe.

It is difficult to differentiate encephalitis and meningitis, as they are most frequently combined. One could say that the importance of central nervous system symptoms is in favor of encephalitis rather than meningitis. A definition of encephalitis was published, in order to allow comparisons between studies at an international level [1]:

- A major criterion is required: the patient should present with altered mental status (defined as decreased or altered level of consciousness, lethargy, or personality change) lasting ≥24 h with no alternative cause identified.
- Minor criteria are required—two for possible encephalitis and three or more for probable or confirmed encephalitis:
  - Documented fever ≥38 °C (100.4 °F) within the 72 h before or after presentation
  - Generalized or partial seizures not fully attributable to a preexisting seizure disorder
  - New onset of focal neurologic findings
  - CSF WBC count ≥5/cubic mm

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- Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset
- Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause

9.2 Epidemiology

From 2003 to 2014, 564,916 tuberculosis cases were reported by 27 EU/EEA countries, 83% presenting with exclusive pulmonary infection and 17% with extrapulmonary disease. Neurological involvement was reported as 3% of extrapulmonary infections [2].

In France, a study about 253 infectious encephalitis [3] reported 20 tuberculous encephalitis cases (5% of all cases, 15% of identified cases), sorted as confirmed (60%), probable (20%), and possible (20%).

The refugee crisis is mixing populations. A Spanish study, from 2004 to 2013, reported that, among 2426 immigrants, 2.85% of sub-Saharan patients presented with extrapulmonary tuberculosis, as well as 11% of patients coming from Maghreb, 4.4% of patients coming from Eastern Europe, and 1.5% of patients coming from Latin America [4].

In two European studies, one in France [5] and the other one in UK [6], tuberculosis appeared to be 15% of encephalitis with an aetiological diagnosis (8% of all cases including non-identified cases) and 12% of demonstrated infectious encephalitis, respectively. In the French study, neurotuberculosis was identified in patients who most likely had ancient infections but recent clinical resurgence. In the California Encephalitis Project, tuberculosis accounted for less than 1% of enrolled cases [7]. These discrepancies are related to the local epidemiology of tuberculosis.

9.3 Pathophysiology

The brain is colonized via a bacteremia, the primary infection being located in the respiratory tract, with or without symptoms. A small number of bacilli enter the bloodstream and spread throughout the entire body. The brain is one of the possible organs for metastasis.

In the brain, *Mycobacterium tuberculosis* acts like in the lung [8–10].

1. Three cell types are essential for protecting from *M. tuberculosis:*
   - Macrophages, phagocytizing bacteria. When ingested by macrophage, *M. tuberculosis* is located in phagosome. Then its urease stops acidification, so it prevents bacilli to be digested in the cell. In phagosome, antigens are presented to the class II major histocompatibility complex and stimulate CD4+ T

cells. As antigens don't diffuse into cytoplasm, they are not presented to class I major histocompatibility complex and by the way don't stimulate CD8+ T cells.
- CD4+ T lymphocytes secreting cytokines TH1 (IFN-alpha).
- CD8+ T lymphocytes secreting IFN-alpha able to lyse infected macrophages.

2. Granuloma is made by:
   - In its center, macrophages leading to multinucleated giant cells
   - In periphery, T and B lymphocytes

Necrosis can occur in the center, leading to caseous abscess, able to calcify or to liquefy.

The delay between primary infection and neurological presentation varies from some weeks (acute infection) to years (resurgence).

9.4 Anatomopathology

- The meningeal exudate characteristics are:
  - Most frequent and important in the brain base
  - Surrounding cranial nerve origins
  - Invading choroid plexus
  - May spread to ventricles, lobes
- Inflammation and necrosis are probably related to hypersensitivity reaction.
- Vascular lesions are correlated to the magnitude of meningeal lesions and may lead to fibrinous necrosis as well as thrombosis.

9.5 Clinical Presentation

Encephalitis is defined according the international definition [1], described above.

Typically, patients with neurotuberculosis present with some specific symptoms or circumstances. Delay for diagnosis has to be considered, most frequently related to the mild initial neurological presentation of a lot of cases, when compared with other infectious encephalitis. In a study reporting patients managed in France [3], the median delay between the onset of general and neurological symptoms was significantly longer for tuberculosis cases than for other encephalitis (10 days vs. 2; $P < 10^{-10}$). In this study only 20% of patients had a history of previous tuberculosis. None was associated with an ongoing tuberculous pneumonia. Eleven (55%) patients had stayed in the ICU, 10 of whom with mechanical ventilation.

9.6 Biological Features

9.6.1 CSF

Protein level in CSF is higher in tuberculosis patients than in other aetiologies [3]. The median CSF protein level was significantly higher for tuberculosis cases than for other encephalitis cases (2.1 g/L vs. 0.8 g/L, $P = 0.002$). The median pleocytosis was 150 cells/mm3 (range 4–640 cell/mm3). The glycorrhachia/glycemia ratio was low for 16/18 (89%) patients.

Diagnostic test sensitivity data reported are extrapolated from published data on tuberculous meningitis, because very few studies have been performed on encephalitis [11].

A prospective study of 132 tuberculous meningitis adult patients was performed in Vietnam in 2004. Authors obtained a microbiological diagnosis for 82% of patients. The microscopic examination and CSF cultures were positive for 58 and 71% of cases, respectively [12]. In this study, the drivers for the CSF microscopic examination sensitivity were (i) the number of samples per patient (sensitivity ranged from 37% to 87% when one to three CSF samples were analyzed, despite treatment initiation), (ii) the volume of CSF available (from 10 to 15 mL at best), and (iii) the examination of the CSF sediment. In a large European retrospective study involving 14 countries [13], 506 patients presenting with confirmed (a positive microscopic examination and/or a positive CSF culture on specific medium and/or a positive PCR) central nervous system tuberculosis were selected. Authors observed that CSF cytology yielded 320 ± 492 NC/mm3, with a predominance of lymphocytes (67 ± 26%), CSF protein level at 3.1 ± 4.2 g/L, and CSF glucose level/glycemia ratio of 0.28 ± 0.15. Culture sensitivity on Lowenstein medium was 72.6% and the sensitivity of the microscopic examination was 27.3%. This low performance of direct examination is probably due to the low inoculum of *M. tuberculosis* in CSF, the bacteria being located in cells of tissues, not in the fluid.

Several authors suggested using CSF adenosine deaminase (ADA) titration as a criterion to discriminate tuberculous meningitis from other bacterial meningitis types, but the performance of this test is debated. The authors of a meta-analysis reported sensitivity and specificity of ADA titration of 79 and 91% in the diagnosis of central nervous system tuberculosis, with positive and negative likelihood ratio of 6.85 and 0.29, respectively [14]. Another study [15] reported a lower sensitivity for ADA titration (55%). Nevertheless, the recent European study reported a positive ADA in routine practice in only 41/137 cases (29.9%) [13]. So far, this test is not recommended in recent guidelines [16].

PCR could be a better tool for diagnosing CNS *M. tuberculosis* infection. Unfortunately, there is no standardized PCR for CSF, so far, and performance of this test is linked to the experience of the microbiological laboratory and the used marketed PCR. The authors of a 2013 study of 235 South African patients presenting with *M. tuberculosis* meningitis [17] observed that the quantitative Xpert MTB/RIF PCR, versus culture and/or Amplicor PCR, was associated with a better

sensitivity than that of a clinical score or the CSF microscopic examination (Gram and auramine staining): 62% versus 30% and 12%, respectively ($P = 0.001$). Sensitivity was better when the CSF sample had previously been centrifuged (82% vs 47%), which required 3 mL of CSF (instead of 1 mL). South Africa being an endemic country for tuberculosis, PPV and NPV of the Xpert MTB/RIF test were 90 and 77%. A meta-analysis of eight studies was published in 2014 and revealed that the sensitivity and specificity of the Xpert MTB/RIF test in CSF, as compared with culture, were 81 and 98%, respectively [18]. The authors of the multicenter European study observed 57.3% sensitivity for *M. tuberculosis* PCR [15]. This sensitivity was measured using the analysis of heterogeneous PCR techniques: PCR-hybridization (Cobas®Amplicor, Grenzach-Wyhlen, Roche, Germany), RT-PCR (ProbeTec®, Becton Dickinson, Oxford, UK), GeneProof® (GeneProof, Brno, Czech Republic), and GeneXpert® (Cepheid, Sunnyvale, CA, USA),which makes impossible evaluating the sensitivity of each of these techniques. The European authors also highlighted the possibility of performing a blood IGRA test (QuantiFERON®-TB Gold In-Tube test) and reported good results: 37 positive results out of 41 tested (sensitivity of 90.2%).

9.7 Imaging

Brain MRI is the best tool for diagnosis of encephalitis, and CT scan should be used only when MRI is impossible [16].

There are no specific images for tuberculous encephalitis, except in case of brain abscess or granulomatous lesions. In the recent study [3], CT scan and MRI were normal on admission for 8 patients out of 17, meaning it is impossible to reject diagnosis of tuberculosis in case of normal images.

9.8 Treatment

9.8.1 Standard

Delays in initiating the antimicrobial treatment in encephalitis tuberculosis patients are associated with an increased mortality and a risk of neurological sequelae [19]. An empirical treatment is most frequently initiated because of the difficulty in establishing the final diagnosis (based on bacteriological or histological data) and of the poor sensitivity of rapid diagnostic tests [20]. Before confirmed diagnosis, clinical deterioration or rapid improvement should not lead to early discontinuation. One should keep in mind that specific antituberculous treatment may be associated with long onset of action, especially in patients presenting with severe brain damage. The empirical treatment should thus be administered, once decided, for the whole

scheduled duration, unless a final alternative diagnosis is established [21]. Some suggested administering intensive 6-month treatments [22]. Nevertheless, the standard recommended treatment is the usual combination of four molecules (rifampicin, isoniazid, pyrazinamide, and ethambutol) administered for 2 months, followed by a dual combination therapy for an overall treatment duration of 9–12 months [23–25]. Unexpected treatment discontinuation is an independent risk factor for mortality in patients presenting with central nervous system tuberculosis [26] that argues in favor of the standard long-term treatment.

Isoniazid is a rapidly bactericidal agent, with a good CSF diffusion [27]. After administration of the usual doses (3–5 mg/kg/day), the obtained CSF concentrations of isoniazid are 10–15 times the minimum inhibitory concentration of *M. tuberculosis* [28]. Several authors suggested increasing isoniazid dosage to more than 5 mg/kg/day, i.e., 10–20 mg/kg/day in children. However, its excellent CSF diffusion does not support this increase in case of susceptible *M. tuberculosis* strain. Isoniazid may thus be administered by rapid intravenous route, associated with pyridoxine supplementation (one dose at a time).

Rifampicin does not reach so important CSF levels: they are <30% of serum concentrations [27]. Nevertheless, mortality related to central nervous system tuberculosis resistant to rifampicin confirms this antibiotic as a key partner in the treatment [29]. Considering its lower central nervous system diffusion, rifampicin has been administered at a dosage of 20 mg/kg/day in children, with good tolerability. Similar doses are used for bone and joint infections, without any safety issue. There is no benefit on mortality when using higher doses of rifampicin (600 mg IV versus 450 mg per os) and moxifloxacin (800 mg versus 400 mg per os) in patients presenting with central nervous system tuberculosis, in addition to a standard treatment with isoniazid, pyrazinamide, and corticoids [30]. Considering the above data, the usual dosage of rifampicin is recommended (10 mg/kg/day).

Pyrazinamide has a good oral bioavailability and a good CSF distribution [31]. It has been used at a dosage of 40 mg/kg/day in children and 30 mg/kg in adults, without exceeding 1.5 g/day [22].

Ethambutol is usually suggested in fourth position [27], despite of its poor diffusion in CNS (especially in the absence of inflammation).

9.8.2 M. Tuberculosis *Resistant*

Fluoroquinolones are an alternative, especially when dealing with resistance or contraindication to one of the molecules included in the "usual" four-drug combination. However, they must be avoided in pregnant or breastfeeding women, as well as for long treatment durations in children [32]. Among fluoroquinolones, moxifloxacin is supposed to have the best activity [33–35]. For single resistance to isoniazid (high-level resistance), it is recommended to replace isoniazid with a fluoroquinolone, for 2 months, and then to continue with a three-drug combination with rifampicin,

pyrazinamide, and a fluoroquinolone for an overall treatment duration of 12 months. For low-level resistance to isoniazid, the agent should keep on being prescribed nonetheless. For single resistance to rifampicin, it is recommended to replace rifampicin with a fluoroquinolone, for 2 months, and then to continue with a three-drug combination with isoniazid, pyrazinamide, and a fluoroquinolone for a total duration of 18 months [23]. Linezolid has also been successfully used [36], but it is restricted to cases of multidrug-resistant strain when combined with second-line treatments.

9.8.3 Adjuvant Therapies

Corticoids may improve the outcome related to noninfectious disorders (brain edema, vasculitis). The addition of a corticoid therapy is based on the extrapolation of findings from studies on tuberculous meningitis that suggested that non-HIV-infected patients must receive corticoids with an antituberculosis treatment, regardless of disease severity [26, 37]. The usual recommended dosages of dexamethasone or prednisolone are 0.4 mg/kg/day for adults and 0.6 mg/kg/day for children. The corticoid therapy is usually administered for 4 weeks, followed by a progressive weaning off over 4 weeks. British guidelines recommend using dexamethasone 0.4 mg/kg/day when neurological signs are observed and 0.3 mg/kg/day in the absence of consciousness disorder or focal neurological signs [23].

In case of persistent cerebral edema despite the administration of corticoids or for immune reconstitution inflammatory syndrome (IRIS), some reported clinical case studies with the use of interferon gamma [38], infliximab (anti-TNF) [39], and thalidomide [40]. Acetyl salicylic acid could have an anti-inflammatory action on mycobacterial infections (inhibiting the expression of eicosanoids and pro-inflammatory TNF) [41]. The authors of two recent studies showed that acetyl salicylic acid reduced the incidence of hemiplegia, stroke, and death in patients presenting with tuberculous meningitis (especially with genotype *LTA4H*) [42, 43].

9.8.4 Surgery

In case of tuberculous encephalitis, hydrocephalus and brain abscesses are the main indications for urgent neurosurgery. It aims at reducing intracranial pressure and bacterial inoculum in case of brain abscesses [44]. Surgical drainage may also be a diagnostic tool (histology, culture, and *M. tuberculosis* antimicrobial susceptibility testing). External ventricular drainage should be urgently performed when life-threatening hydrocephalus is suspected.

9.9 Outcome, Prognosis

In the French study [3], they did not include patients infected with multidrug-resistant strains. Nevertheless, six (33%) patients died during hospitalization. Ten out of 12 (78.6%) had persisting neurological symptoms on discharge. Despite non-multiresistant MT strains, the case fatality rate among tuberculous encephalitis patients was high in this series, compared to other aetiologies. The case fatality rate in other aetiologies (including HSV) was 9% that was a significative difference.

Authors of a multicentric multinational study [45] propose a score for unfavorable outcome of tuberculous meningitis. Unfavorable outcome was reported in 33% of patients, strictly similar to the one observed in encephalitis, that is, quite a validation of both findings. They used the following items to provide a severity index, having a linear correlation with the outcome: altered consciousness, altered consciousness plus nausea, vomiting, diabetes mellitus, immunosuppression, neurological deficit, hydrocephalus, and vasculitis. This score is not validated in encephalitis, but it is probable it could be, and anyway it is a basis, so far, for an evaluation of prognosis.

Despite management in a high-income country, tuberculous encephalitis presents with a poor outcome, even in case of sensitive strains.

9.10 Conclusion

Tuberculous encephalitis is still a burden in high-income countries. It is a frequent aetiology, difficult to assess, with a poor income despite an adequate treatment.

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Chapter 10
Spinal Tuberculosis

Ghaydaa Ahmed Shehata

10.1 Introduction

Spinal infections include infections primarily affecting (1) the spinal cord; (2) nerve roots and meninges; or (3) the vertebrae, intervertebral discs, and epidural space. They are broadly classified as pyogenic or nonpyogenic, with the former category including vertebral osteomyelitis and discitis, while parasitic, fungal, and tuberculous infections constitute the latter category.

10.2 Definition

Tuberculosis (TB) is one of the oldest pathological conditions that affect mankind. It can affect several tissues outside the lungs. Five percent of TB cases affect the skeletal system, with 50% of those being located within the vertebral column [1] and causing a kind of tuberculous arthritis of the intervertebral joints. Spinal TB (STB) is also known as *Pott disease* (or *Pott's disease*), named after Percival Pott, who published the first description of it in 1779 [2].

10.3 Epidemiology

Tuberculosis is a global health problem, affecting one third of the world's population [3]. It is a widespread disease, with 8.7 million new cases annually, and worldwide rates of TB have increased in parallel with the incidence of acquired

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immunodeficiency syndrome (AIDS) [4]. The increase in TB has been witnessed not only in Africa and Asia but also in European countries. In addition, TB ranks second, just after human immunodeficiency virus (HIV) infection, among infectious causes of mortality. Hence, TB remains an important cause of morbidity and mortality worldwide [5]. Turkey has been reported to be a low-incidence country for TB [3].

When extrapulmonary TBSpinal tuberculosis (STB)epidemiology is taken into consideration, 10–35% of all TB cases [6]. In 2016 it was estimated that STB accounted for around 2% of all cases of TB and around 15% of extrapulmonary TB cases [7].

10.4 Risk Factors for Developing Spinal Tuberculosis

There are many predisposing factors for STB, including previous TB infection and malnutrition [8]. Population groups with an increased risk of STB include immunecompromised persons (with AIDS, lymphoma, leukemia, or organ transplants), diabetic persons, children, elderly persons, alcoholics, persons with a low socioeconomic status, persons with poor treatment compliance, migrants from developing countries, prisoners, nursing home residents, health care workers, and homeless people [9, 10]. In addition, hematological seeding from an infectious focus in the skin, genitourinary tract, gastrointestinal tract, or respiratory tract is considered an important risk factor for STB [11].

10.5 Pathophysiology

There are two types of STB: the classic form (or spondylodiscitis) and an increasingly common atypical form, which is spondylitis without disk involvement [12]. In adults, involvement of an intervertebral disc is secondary to spread from an adjacent infected vertebra, while in children it can primarily be due to the vascularized nature of the intervertebral discs. The basic lesion in Pott's disease is a combination of osteomyelitis and arthritis, usually affecting more than one vertebra. The anterior aspect of the vertebral body adjacent to the subchondral plate is commonly involved [13]. STB can include any of the following: progressive bone destruction, leading to vertebral collapse and kyphosis, spinal canal narrowing by abscesses, cold abscess formation (due to extension of infection into adjacent ligaments and soft tissues), or granulation tissue or direct dural invasion, resulting in spinal cord compression. These events lead to different neurological deficits [8, 12, 13].

10.6 Diagnosis

The diagnosis is based on the history, imaging studies of the spine, chest radiography, computed tomography (CT) of the chest, and laboratory values such as the white blood cell count and purified protein derivative tests.

10.6.1 Clinical Picture

10.6.1.1 Clinical Course

The involvement of spinal vertebrae results from hematogenous spread of *Mycobacterium tuberculosis* into the cancellous bone tissue of the vertebral bodies [7]. The primary infection site comes from either a pulmonary focus or another extrapulmonary focus, such as the gastrointestinal tract or lymph nodes [8].

10.6.1.2 Clinical Presentation

Delays in diagnosis of STB are common [7]. Patients with STB may present with a wide variety of symptoms [14].

The average time from presentation to diagnosis is 1 year and 7 months. Typically, the onset of symptoms is insidious, and the disease progression is slow. The duration of symptoms prior to diagnosis may range from 2 weeks to several years [15].

With regard to sex predilection in STB, 53% of STB patients are male [7].

The clinical presentation and findings of physical examinations depend on the site and stage of the disease, the presence of complications, and constitutional symptoms [16].

The most commonly reported symptoms are focal back pain, fever, weight loss, and neurological abnormalities such as motor or sensory root affection of the bowel/bladder dysfunction, and paraplegia [7].

Also, the patients have systemic symptoms of active TB, including cough, shortness of breath, fevers/chills, and night sweats.

10.6.1.3 Complications After Spinal Tuberculosis

The incidence of neurological deficit varies from 23% to 76% [7].

Complications include syringomyelia, permanent neurological deficits, and spinal osseous defects [17]. Paraplegia is considered the most devastating complication of STB.

10.6.1.4 Laboratory Tests

Hematological investigations such as a complete blood count, erythrocyte sedimentation rate, enzyme-linked immunosorbent assay, and polymerase chain reaction (PCR) are needed in the case of STB [7].

Microbiological evidence includes at least one of the following: isolation of *M. tuberculosis* in blood, bone, bone marrow, deep soft tissue, and/or (paravertebral, epidural, or psoas) abscess specimens; and positive microscopy for acid-fast bacilli from bone, bone marrow, deep soft tissue, and/or a (paravertebral, epidural, or psoas) abscess, or any sterile body tissue. Bone tissue or abscess samples stained for acid-fast bacilli, mycobacterial organisms isolated from culture, and CT-guided or ultrasonography-guided needle biopsy or surgical biopsy are also widely used [7, 15, 18]. That can be done by use of Ziehl–Neelsen staining. In addition, rapid culture by use Ziehl–Neelsen staining by using PCR for detection *M. tuberculosis complex* [3, 7, 19].

10.6.1.5 A Rapid Biomarker-Based Nontissue-Based Test

The accuracy of tools for immunological diagnosis of tuberculosis, using two mycobacterial proteins—culture filtrate protein-10 and early secretory antigenic target-6—has been evaluated [20]. With high sensitivity and specificity, the enzyme-linked immunospot (ELISPOT) assay, using CFP10/ESAT6 fusion protein as an antigen, is an effective technique for auxiliary diagnosis of STB [20]. These immunodiagnostic tests, the whole-blood interferon-g (IFN-g) enzyme-linked immunosorbent assay QuantiFERON-TB Gold (Cellestis Ltd., Chadstone, VIC, Australia), and the enzyme-linked immunospot assay T-SPOT.TB (Oxford Immunotec, Oxford, UK), can quantitatively measure IFN-g production by lymphocytes specific to *M. tuberculosis*–specific immunodominant antigens, which are encoded by the RD1 region of the pathogen. Another commercially available IFN-g release assay (IGRA), the QuantiFERON-TB Gold in-tube assay (QFTGIT) (Cellestis Ltd.), is able to measure IFN-g production specific to the immunodominant TB antigens early secretary antigenic target-6 and culture filtrate protein-10 [7].

10.6.1.6 Imaging Diagnosis

Spinal TB commonly manifests as tuberculous meningitis (TBM) and rarely as intramedullary tuberculoma [9]. However, plain radiography is performed initially in patients suspected to have STB, and plain radiograph images show a birds-nest appearance characteristic of an aneurysmal phenomenon [21].

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) abnormalities include spinal lesions that originate from the vertebral endplate, involve the anterior vertebral body corner, show evidence of subligamentous spread, exhibit multiple vertebral bodies but preserved disks, and show extensive paraspinal abscess formation, abscess calcification, and vertebral destruction or vertebral body collapse [9, 21].

In addition, there is extensive paraspinal abscess formation and abscess calcification [9]. CT is more effective for defining the shape and calcification of soft tissue abscesses than plain radiography, because CT provides much better visualization of the bony details of irregular lytic lesions, sclerosis, disk collapse, and disruption of bone circumference.

For radiolucent lesions to be visible on plain radiographic images, there must be 30% bone mineral loss [15].

Positron emission tomography (PET) can be useful in differentiating between STB and other pyogenic spondylitis [22]. However, MRI can be used for early detection of STB, which can reduce the complications of STB. A confirmatory diagnosis can be made only on the basis of biopsy or culture results [9].

10.7 Classification of Spinal Tuberculosis

Kumar introduced a four-point classification for posterior STB, based on the site of involvement and the stages of the disease [23]. One of the most important limitations attributed to this classification system is that it includes only posterior STB, which is relatively rare.

Mehta and Bhojraj introduced a new classification system for STB, using MRI findings. They classified patients into four groups according to the surgical technique employed. Group A consisted of patients with stable anterior lesions and no kyphotic deformity. Group B consisted of patients with global lesions, kyphosis, and instability. Group C patients had anterior or global lesions along with a high operative risk for transthoracic surgery, due to medical comorbidities and probable anesthetic complications. Finally, group D patients had isolated posterior lesions that needed only posterior decompression [23, 24]. This classification categorizes only thoracic lesions, which is the most important limitation of this system [13].

10.8 Treatment

Antituberculosis drugs have a main role in the recovery and response of patients with STB [25]. The efficacy of these drugs has been shown in several studies of STB treatment in the absence of a neurological deficit, instability, and deformity,

regardless of the presence of a paravertebral abscess [26]. Adequate and early pharmacological treatment can prevent severe complications [27]. A combination of rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 months, followed by a combination of rifampicin and isoniazid for a total period of 6, 9, 12, or 18 months, is the protocol most frequently used for treatment of STB [17, 26, 27]. Short-course chemotherapy regimens have been demonstrated to have excellent results except in patients younger than 15 years and those with an initial angle of kyphosis of more than 30 degrees and whose kyphosis increases substantially [28]. Patients who receive medical management alone may receive CT-guided drainage of the target lesions [7].

Multidrug-resistant TB is defined as an organism that is resistant to rifampicin and isoniazid [25]. Such resistance is detected if there is a lack of clinical or radiological improvement, development of a new lesion or a cold abscess, or an increase in bone destruction despite medical treatment for 3–5 months [25]. Multidrug-resistant TB is a global concern; it is encountered in 3% of all new cases and in 12% of retreatment cases [13]. The recommended treatment for multidrug-resistant TB is an average of six anti-TB drugs for at least 24 months [29]. The most recent World Health Organization (WHO) guidelines recommend use of five drugs that are expected to be effective in the initial intensive phase and four drugs that are likely to be effective in the continuation phase. The duration of the initial phase is 6–9 months, and the total treatment period is 20–24 months [29]. Close monitoring of patients for development of adverse reactions is necessary [25, 29].

10.8.1 Surgical Treatment

The neurological status at the time of presentation is a critical factor for treatment decision making and patient outcomes. If the imaging results suggest that STB is present, the decision regarding operative management should be based on assessment of the risk of failure of medical treatment, according to the grading system for spondylodiscitis [30]. Surgery is often required for decompression [31], kyphosis correction, and maintenance of spinal stability [31, 32]. There is controversy as to the ideal surgical approach. An anterior approach allows direct access to the focus of infection, which is helpful for debridement. However, surgery with a single anterior approach could lead to unsatisfactory outcomes in terms of kyphosis correction and maintenance of spinal stability [33]. Surgery with a single posterior approach shows advantages in kyphosis correction and maintenance of spinal stability, but it does not allow complete debridement of an infected lesion in front of the vertebrae [32]. Thus, a combination of anterior debridement/bone grafting and posterior instrumentation, which overcomes the drawbacks of surgery via a single anterior or posterior approach alone, has become a common choice for treatment of STB [32]. With the development of minimal invasive spinal surgery, a technique of posterior percutaneous instrumentation is also employed to enrich the surgical methods of anterior debridement/bone grafting/posterior instrumentation [32].

10.8.2 Prognosis

The determinants of the success or failure of multidrug-resistant TB treatment are (1) progressive clinical improvement at 6 months following chemotherapy; (2) radiological improvement during treatment; (3) disease with *M. tuberculosis* strains that are resistant to use of up to three anti-TB drugs and use of up to four second-line drugs; and (4) no change in the drug regimen during treatment [29].

Some prognostic factors need to be defined before surgical intervention. Kyphosis can be defined as the occurrence of a negative Cobb angle, which can appear at the lumbar level on the basis of bone destruction. With regard to the physiological spinal curve, the lumbar vertebrae maintain a lordotic curve, with a Cobb angle range of 30–50°. In 137 cases with kyphosis caused by STB, the lordotic curve of lumbar vertebraeSpinal tuberculosis (STB)prognosis became kyphotic and the Cobb angle changed to a negative value as a result of bone destruction [30]. Yao et al. [34] identified nonparalysis, a shorter symptom duration, fewer involved vertebrae, and percutaneous instrumentation as favorable prognostic factors for recovery postoperatively. In the early postoperative stages (1–3 months), patients treated with percutaneous instrumentation achieved higher Japanese Orthopedic Association (JOA) scores than those treated with open instrumentation, but no significant difference in JOA scores was observed in the longer term (6–24 months). Moreover, the patients treated with percutaneous instrumentation had a shorter operation time.

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Chapter 11
Urogenital Tuberculosis

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Take-Home Message
Urogenital tuberculosis (TB) seems to be a rare disease, but it is mostly overlooked. Urogenital TB is contagious and it is a reason for infertility. Modern techniques allow diagnosing this infection in time, and optimal management may save organs.

11.1 History

The first note on urogenital tuberculosis (TB) was made by Porter in 1894 [1]; this time the term "urogenital TB" was accepted. In 1937 Wildbolz [2] suggested the term genitourinary TB. There was no particular reason to change the term, nevertheless the medical society approved the new term and since we had both terms. However, the term urogenital TB is more correct, because kidney TB, which is usually primary, is diagnosed more often than genital TB.

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11.2 Definitions

Urogenital TB (UGTB) may be defined as an infectious inflammation of any urogenital organ (kidney, urinary tract, and/or male or female genitals), caused by *Mycobacterium tuberculosis* (Mtb) or *Mycobacterium bovis* (*M. bovis*).

Genital TB (GTB) may be defined as an infectious inflammation of the female or male genitals, caused by *Mtb* or *M. bovis.*

Urinary tract TB (UTTB) is an infectious-allergic inflammation of the upper and/or lower urinary tract, always secondary to kidney TB (KTB) and should be considered a complication of KTB.

Female genital TB is not included in this chapter.

11.3 Classification

UGTB can be classified into the following entities:

11.3.1 Kidney Tuberculosis (KTB)

The infectious inflammation of the kidney parenchyma, caused by Mtb or *M. bovis* There are four stages to be considered:

Stage 1: TB of kidney parenchyma (nondestructive form, KTB-1) is subject to conservative therapy only. KTB-1 has minimal lesion without destruction and full recovery is possible by anti-TB drugs. Intravenous urography (IVU) is normal. Urinalysis in children is often normal, but in adult low-level leukocyturia may be found. Usually patients have no complaints and are diagnosed accidentally. Mtb detection in urine is always necessary for diagnosing kidney TB stage 1.

Stage 2: TB papillitis (small-destructive form, KTB-2) may be uni- and bilateral, solitary, and multiple. KTB-2 should be treated with anti-TB drugs, but if complicated, reconstructive surgery is indicated. Mtb is not detected in all cases and may be resistant.

Stage 3: Cavernous kidney TB (destructive form, KTB-3). KTB-3 has two ways of pathogenesis, from TB of parenchyma or from papillitis. The first way means development of a subcortical cavern without connection to the collecting system. The clinical manifestation of a subcortical cavern is similar to a renal carbuncle; thus the diagnosis is usually made after the operation. The second way is the destruction of the papilla until a cavern is developed. Complications develop in more than half of the patients. Full recovery by anti-TB drugs is impossible, and surgery is generally indicated.

Stage 4: Polycavernous kidney TB (widespread-destructive form, KTB-4). Recovery with anti-TB drugs only is impossible; surgery is necessary, basically nephrectomy.

Complications of kidney TB are chronic renal failure, fistula, and high blood pressure.

11.3.2 Urinary Tract TB (UTTB)

Urinary tract TB (UTTB) includes TB of renal pelvis, ureters, bladder, and urethra. UTTB first appears as an edema; the next stages are infiltration, ulceration, and fibrosis. UTTB is always secondary to KTB. UTTB can be subclassified in the following parts:

11.3.2.1 TB of Ureter

TB of the ureter usually develops in the lower third, but multiple lesions are possible too.

11.3.2.2 TB of the Bladder

TB of the bladder is divided into four stages [3]:

Stage 1 – tubercle-infiltrative
Stage 2 – erosive-ulcerous
Stage 3 – spastic cystitis, which in fact means overactive bladder
Stage 4 – contracted bladder up to full obliteration

The first two stages should be treated by standard anti-TB drugs, the third stage with standard anti-TB drugs and trospium chloride, and the fourth stage is indicated for cystectomy with urine diversion or bladder replacement surgery.

There is one more form of bladder TB, the iatrogenic BCG-induced bladder TB, which develops as a complication of BCG therapy for bladder cancer.

11.3.2.3 TB of Urethra

TB of the urethra is nowadays not a frequent complication; usually it is diagnosed at the stage of a stricture.

11.3.3 Male Genital Tuberculosis (MGTB)

Male genital tuberculosis (MGTB) is subdivided into four categories:

11.3.3.1 TB Epididymitis (Uni- or Bilateral)

Bilateral TB epididymitis is always secondary to prostate TB. Isolated TB epididymitis was found in 22% as accidental surgical finding [4].

11.3.3.2 TB Orchiepididymitis (Uni- or Bilateral)

TB of the testis is always secondary to infection of the epididymis, which in most cases is blood-borne because of the extensive blood supply of the epididymis, particularly the lobus minor. In 62% of patients with orchiepididymitis, KTB is diagnosed as well. Every third patient has bilateral lesions. In about 12% of cases, the disease is complicated by fistulas [4, 5].

11.3.3.3 TB of the Prostate (Infiltrative or Cavernous Forms)

Prostate TB is an often underdiagnosed disease. Three-quarters of men, who died from any form of TB, had prostate TB which was mostly overlooked until autopsy [6]. In 79% of patients, prostate TB was accompanied by KTB, in 31% by TB orchiepididymitis, and in 5% an isolated prostate TB was diagnosed [3–5].

11.3.3.4 TB of Seminal Vesicles

TB vesiculitis is secondary to prostate TB and leads to infertility. As drainage of caseous ejaculate is difficult, TB of seminal vesicles exhibits a tendency to calcification.

11.3.3.5 TB of the Penis

Penile TB is rare but can occur after sexual intercourse with infected females [7] or via a direct infection through a penile wound during ritual circumcision. Penile lesions present as ulcers on the glans or penile skin. Also it may be as a complication of BCG therapy [8].

11.3.3.6 Complications of MGTB

Complications of MGTB are strictures, fistula, infertility, and sexual dysfunction.

11.3.4 Generalized Urogenital Tuberculosis (gUGTB)

Generalized urogenital tuberculosis (gUGTB) simultaneous lesions of the kidney and the urinary and genital organs; gUGTB is always considered a complicated form of TB.

Etiology of Urogenital TB
In a big family of *Mycobacteria*, *Mtb and M. bovis* are combined in the *mycobacterial complex* and are obligatory pathogens for the human organism. In 80–95% of cases UGTB is caused by Mtb, but as TB is an anthropozoonotic infection, *M. bovis* is also an etiological agent of TB [9–11]. Bacillus Calmette-Guérin (BCG), which is in fact an attenuated *M. bovis*, is widely used for therapy of superficial bladder cancer. BCG therapy may be complicated by iatrogenic BCG-induced UGTB – mainly bladder or prostate TB – but in rare cases BCG sepsis has been diagnosed [12–15].

11.4 Diagnosis

11.4.1 Clinical Features

Clinical features of UGTB are non-specific and instable and depend on many factors. This is one of the reasons for late diagnosis. Most common complaints are flank pain (up to 80%) and/or dysuria (up to 54%). If the urinary tract is involved, then renal colic (24%) and gross hematuria (up to 20%) may occur. Prostate TB manifests itself by perineal pain and dysuria and in half of the cases by hematospermia. TB epididymo-orchitis always starts from epididymitis; edema, swelling, and pain of the scrotal organs are most often the first symptoms. In 68% of cases, there is an acute debut of the disease. Nevertheless, in 32–40% of patients, the disease has a chronic or asymptomatic course [3, 16–20].

11.4.2 Physical Examination

Special attention should be paid to any fistula. Scrotal and perineal fistulae are highly suspicious for TB [18]. In the acute course of TB epididymitis, a hard, painful, enlarged epididymis intimately welded with the testis can be palpated. In

chronic cases epididymis is still hard, enlarged, and painless but usually with a clear border to the testis. In 35–40% of cases, the findings are bilateral. Digital rectal examination of the patient with prostate TB shows a moderately enlarged tuberous prostate with weak pain [4, 5, 20].

11.4.3 Laboratory Tests

All patients with UGTB should be screened for pulmonary involvement and HIV infection.

11.4.3.1 Urinalysis and Culture Tests

Leukocyturia is found in 90–100% of patients with KTB and hematuria in 50–60% [3]. Before the "antibiotic era," sterile pyuria was a specific sign of KTB, but now up to 75% of patients have non-specific pyelonephritis alongside with KTB and therefore uropathogens and Mtb may be found in urine together [17–20]. The diagnosis of UGTB is absolutely confirmed when Mtb is detected, but in recent years Mtb could be found only in half of TB patients. Therefore, in patients suspected of having UGTB, but without documented evidence of Mtb, the diagnosis of urogenital TB has to be made on the basis of other features, such as skin test, histological findings, caverns revealed by intravenous pyelography, sterile pyuria, etc. [3, 21].

A microbiological confirmation of the diagnosis of UGTB may be made by culturing of *Mtb* (from an appropriate clinical sample such as urine, pus, semen, or tissue biopsy) or by identification of *Mtb* DNA using the rapid molecular diagnostic test, the GeneXpert® MTB/RIF assay. Due to the slow growth rate, conventional solid culture systems including Löwenstein-Jensen slant or Middlebrook 7H11 agar plates always require 8 weeks of incubation before a negative result can be reported. Unfortunately, today standard culture on standard media has low efficiency for UGTB patients. One of main reasons for false-negative results is nonoptimal empiric therapy for UTI, when a patient with UGTB masked by non-specific UTI is treated with amikacin and fluoroquinolones. Both these drugs negatively influence on a growth of Mtb.

What modern technologies of rapid MTB identification are available? First of all molecular genetic methods in TB diagnosis, which include:

- Detection of Mtb with different polymerase chain reaction (PCR) techniques (flash, real-time, Hain Lifescience)
- Determination of drug resistance of the pathogen (I–II line anti-TB drugs)
- Identification of type, strain of pathogen, and genotype determination of mycobacteria isolated from a patient (*M. tuberculosis*, non-tuberculous mycobacteria)

Also BACTEC MGIT 960 system, a fully automated and nonradiometric culture system, has been recommended for faster mycobacterial isolation from clinical specimens. The culture is monitored with the oxygen-quenching fluorescent sensor technology every 60 minutes, which provides a satisfactory performance in a short laboratory turnaround time when compared with conventional methods. The BACTEC MGIT 960 is therefore widely considered as the gold standard for the diagnosis of TB. But even this modern method may give false-negative results. Growth of Mtb in BACTEC MGIT 960 can go undetected, especially the most aggressive Beijing strain [3, 21].

11.4.3.2 Histology

Histological investigation of biopsy or surgical material may reveal epithelioid granuloma and caseous necrosis, both of which are soon replaced by fibrous tissue especially after suboptimal previous therapy. Prostate biopsy should only be performed after urethrography in order to exclude caverns [22, 23].

Fine-needle aspiration cytology (FNAC) may be useful to diagnose TB of the external male genitals [4]. However, scrotal surgery including histology should always be considered if there is suspicion that the mass is malignant. Fatal complications due to fulminant generalization of TB have occurred after biopsies performed in non-treated patients with active UGTB.

11.4.3.3 Imaging

Ultrasonography Ultrasound investigation may give indirect evidence of urogenital TB only. As prostate TB is accompanied by KTB in 79% of cases [24], pathological findings detected by renal ultrasound in patients with "chronic prostatitis" are very suspicious for urogenital TB. TB epididymitis and orchitis present as diffusely enlarged lesions, which may be homogeneous or heterogeneous and can also occur as nodular enlarged heterogeneously hypoechoic lesions [24]. Transrectal ultrasound may reveal hypo- and hyperechoic lesions of the prostate, predominantly in the peripheral zone, but also as prostatolithiasis which may be calcified zones of TB inflammation [24].

Radiological examinations are not useful for diagnosis of UGTB in early stages. Intravenous pyelography (IVP) is indicated for patients with leukocyturia and/or abnormalities on ultrasound investigations. Retrograde urethrography should be performed in all patients with GTB to exclude caverns in the prostate. Multi-sliced computer tomography (CT) is more informative. On contrast-enhanced CT scan, TB of the prostate or seminal vesicles can be seen as low density or cavitation lesions due to necrosis and caseation with or without calcification. Without calcification, the findings may be similar to pyogenic prostatic abscesses [25, 26].

Endoscopy Generally, instrumental interventions are of limited value for the diagnostic work-up in UGTB. However, cystoscopy is indicated in all UGTB patients with dysuria. Any mucosal pathology should be biopsied and investigated both by histology and bacteriology, although the absence of specific findings does not exclude the diagnosis of TB [3].

11.5 Treatment

11.5.1 Chemotherapy

As UGTB is a contagious disease, anti-TB therapy should start as soon as possible. Once a diagnosis of active TB is made, TB drug treatment should follow WHO and specialist society guidelines [27–31].

When the disease is naive and caused by drug-sensitive Mtb, first-line anti-TB drugs should be prescribed. When there is resistance of Mtb to first-line anti-TB drugs or poor tolerance, severe adverse effects, or in case of recurrence of the disease, second or third line of anti-TB drugs are indicated [32].

11.5.2 Most Common Adverse Effects of Anti-TB Therapy

Long-term exposure to anti-tuberculosis medication increases the risk of adverse drug reactions and toxicity. The liver is vulnerable to injury from the first-line anti-tuberculosis drugs [33]. Anti-tuberculosis (anti-TB) drug-induced hepatotoxicity is the most common side effect leading to interruption of therapy. This may result in mortality, long-term morbidity, and reduced compliance to therapy. Older age and poor nutritional status including baseline hypoalbuminemia were independent predictors of development of anti-TB hepatitis [34]. In another study old age, anemia, MDR-TB medication, overweight/obesity status, and smoking history were independent risk factors for anti-tuberculosis adverse drug reactions [35].

Linezolid is one of the few drugs that have shown promise in treating extensively drug-resistant (XDR) tuberculosis and multidrug-resistant (MDR) tuberculosis. Long-term linezolid use is associated with toxicities such as peripheral and optic neuropathies. Diabetes mellitus, especially when uncontrolled, can also result in peripheral neuropathy if a patient receives linezolid [35].

11.5.3 Negative Influence of Tuberculosis and Anti-TB Therapy on Sexual Function

Not only genital forms of TB might have negative influence on female reproductive function. Pulmonary TB is accompanied by menstrual abnormalities in 66% of women. However, after completing anti-tuberculosis treatment, 76% of women with menstrual abnormalities resumed normal menstrual cycles [36, 37].

Anti-TB treatment has a negative effect on the ejaculate: a 2-month course of anti-TB therapy resulted in a decrease of sperm quality by 23.9% and decreased number of actively motile sperm by 10.6% and the number of morphologically normal sperm by 32.3% [38]. To evaluate sexual function, 98 pulmonary TB male patients were enrolled in retrospective study. The intravaginal latency time was estimated before the start of anti-TB therapy and in 3 months of anti-TB therapy. On baseline 14.3% of pulmonary TB patients had ejaculatory disorders, 10.2% had premature ejaculation, and 4.1% had delayed ejaculation. The remaining 85.7% of patients had normal ejaculation [39, 40]. After 3 months of the therapy with four anti-TB drugs (isoniazid, rifampicin, pyrazinamide, and streptomycin), the spectrum of sexual dysfunction changed significantly. The share of patients with normal ejaculation decreased to 61.2%, and the frequency of premature ejaculation doubled (20.4%), and delayed ejaculation was diagnosed 4.5 times more often (18.4%) [40].

Authors emphasized that the proportion of ejaculatory disorders in male patients with pulmonary TB initially was the same as in the general population. They concluded that tuberculosis as a disease doesn't influence the ejaculatory function. But anti-TB therapy with four drugs during 3 months significantly worsened the ejaculatory function for every fourth patient. Authors explained a quadruple increase of frequency of delayed ejaculation by neurotoxicity of some of the anti-TB drugs. So, tuberculosis as a disease doesn't damage the ejaculatory function, but anti-TB therapy does. Future research should look for ways to prevent this complication [40].

In Russia and especially in Siberia, there is currently an epidemic of TB [41]. About two-thirds of newly diagnosed patients are young men, and sexual function and fertility is very important for them. The sexual function was studied in 105 newly diagnosed patients with pulmonary tuberculosis aged 18–39 years [40]. Although no diseases of urogenital system could be found, patients with pulmonary TB showed deterioration of several parameters from sexual desire to orgasm. Patients with widespread cavernous pulmonary TB had higher level of sexual dysfunction than patients with smaller forms of pulmonary TB, and this level had strong correlation with the severity of the sexual dysfunction.

Complex anti-TB chemotherapy improved the fertility of pulmonary TB patients, most likely by arresting the systematic inflammation and reducing intoxication, but even after 6 months of treatment, they had significantly decreased scores on sexual function tests by valid questionnaires [60].

11.5.4 Surgery

Surgical intervention is indicated in advanced cases and for correction of complications. The most relevant surgical interventions are presented in Table 11.1.

All surgical interventions should be performed under coverage of anti-TB therapy. The treatment duration is decided after histological investigation of the removed tissue [42–44].

11.6 Conclusion

Tuberculosis still now is the most important cause of death from an infectious disease in adult worldwide. Urogenital tuberculosis is often missed clinically due to its insidious onset, chronic non-specific symptoms and cryptic and protean clinical manifestations, and lack of clinical awareness. Delays in making a diagnosis result in disease progression, tissue and organ damage, and renal failure. UGTB can present with chronic urinary tract inflammation, hematuria, obstructive uropathy, infertility, and renal or testicular mass and can contribute to the development of urothelial cancer; sterile pyuria today is not typical for UGTB.

Table 11.1 Surgical treatment of urogenital TB

Indication	Surgery
1. Kidney TB	
KTB-3, resistant to standard therapy (notable cavern with pyogenic layer remains, Mtb in urine, pyuria) for 2–4 months	Cavernectomy (partial nephrectomy), optimal – laparoscopically
KTB-4	Nephrectomy, optimal – laparoscopically
2. Urinary tract tuberculosis	
Stricture of ureter, urethra	Standard plastic operation
Bladder TB stage 4	Cystectomy (in male patients – cystoprostatectomy) followed by conduit or bladder replacement
3. TB epididymo-orchitis	
Fluctuation, abscess	Incision of abscess and drainage
Torpid course with low efficiency of conservative treatment for 1–2 months	Epididymo-orchiectomy
4. Prostate TB (normally prostate TB is not indicated for surgery)	
Development of abscess	Drainage of abscess

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Chapter 12
Cardiovascular Tuberculosis

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12.1 General

Tuberculosis (TB) is uncommon in developed countries. But it is still endemic and frequently seen in some areas of Africa and Asia. Besides, the increase in the number of immunocompromised patients, especially with HIV, is responsible for the increase in the incidence of tuberculosis and its complications. According to the World Health Organization (WHO), one third of the world's population has TB infection today, and it is the commonest cause of death among patients with infectious diseases [31].

Extrapulmonary TB is generally found in the pleura, lymph nodes, abdomen, and central nervous system [35]. The cardiovascular system is involved in 1–2% of the patients with TB [4, 27, 30, 33, 35, 50]. The incidence of cardiac TB in autopsies is about 0.25% [33]. It has been shown that the rate of cardiac involvement in patients who died from TB is approximately 2% [43]. Only 0.5% of the patients with extrapulmonary TB have cardiac involvement, and it is more frequently seen in immunocompromised patients [53]. The primary involvement site is pericardium [35, 50, 53]. Other forms of cardiovascular involvement including endocarditis, myocarditis, valvular or coronary involvement, arteritis, and aneurysms are extremely rare [27]. Myocardial involvement by TB may cause arrhythmias, sudden cardiac death, congestive heart failure, and aneurysms. Also, aortitis and arteritis may cause mycotic aneurysms, pseudoaneurysms, and rupture [43].

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12.2 Pericarditis

The pericardium is the most frequently involved cardiac tissue by TB. Pericarditis is seen in less than 1% of the patients with TB [23, 40]. In general, 10–11% of patients with pericarditis have TB etiology [23, 57]. Incidence of TB pericarditis is higher in the endemic areas; it has been reported that TB accounts for 40–70% of the patients with pericarditis in developing countries [40, 43, 50]. In contrast, only 4% of the patients with pericarditis have TB etiology in developed countries [40, 43]. Also, its incidence is higher in the areas where the human immunodeficiency virus (HIV) is epidemic [40, 57].

12.2.1 Pathology

TB pericarditis is always associated with an extracardiac infection focus located anywhere in the body [50]. It spreads to pericardium via three main routes: lymphatic spread (from paratracheal, peribronchial, and mediastinal lymph nodes), hematogenous spread (mainly in immunocompromised patients), or rarely direct contiguous spread from adjacent structures (lungs, pleura, and spine) [40, 43, 50]. Lymphatic and hematogenous spread are the main routes. Pathophysiology of the disease includes four stages: (i) fibrinous exudation with polymorphonuclear infiltration with relatively high number of mycobacteria; (ii) serous or serosanguineous effusions with lymphocytic infiltration (monocytes and foam cells); (iii) absorption of effusion leading to caseating granulomas and pericardial thickening due to fibrin and collagen deposition and fibrosis; and (iv) constrictive scarring with extensive calcification [9, 38, 40]. Fibrosis, adhesion, and calcification of the visceral and parietal pericardium create a rigid and contracted fibrocalcific envelope encasing the heart that restricts diastolic filling and eventually systolic ejection in the constrictive pericarditis stage [40].

TB pericarditis is typically a paucibacillary condition [43]. Proteins of *M. tuberculosis* nestled in the pericardium trigger a T helper subtype 1 (TH-1) lymphocytes-mediated hypersensitivity reaction that stimulates cytokine release [9, 40, 43]. Cytokine release activates macrophages and induces pericardial inflammation and granuloma formation that causes exudative effusion and afterward consequences [40, 43]. Patients with TB pericardial effusions have a cytokine profile (tumor necrosis factor alpha and interleukin 1 and 2) and increased interferon-gamma production suggesting the occurrence of a hypersensitivity reaction orchestrated by the TH-1 lymphocytes [9, 40]. Most frequently implicated cytokine is TNF-α [57]. Cytokines may also cause fever, weight loss, and weakness [57]. Anti-myolemmal antibodies causing cytolysis may have a role in exudative pericarditis [40].

12.2.2 Clinical Properties

Although the course of the disease is mostly insidious and progresses to chronic constrictive pericarditis, acute and fulminant pictures related to pericardial tamponade may also be seen [7, 15]. Tamponade is considered to be the acute complication of TB pericarditis, while constrictive pericarditis is chronic complication [43]. The clinical picture is highly variable and includes acute pericarditis with or without effusion, cardiac tamponade, chronic pericardial effusion, acute constrictive pericarditis, subacute constriction, effusive-constrictive, or chronic constrictive pericarditis, and pericardial calcifications [37, 50]. It is generally manifested as one of four clinical syndromes: acute pericarditis, effusive pericarditis, myopericarditis, or constrictive pericarditis [43]. The usual presentation of the disease is pericardial effusion, constrictive pericarditis, or a combination of effusion and constriction [40]. The disease may progress more aggressively in immunocompromised patients (HIV, etc.); clinical presentations including dyspnea, hemodynamic instability, and myocardial involvement tend to be more severe [43].

12.2.2.1 Tuberculous Pericarditis and Pericardial Effusion

The onset of the disease is mostly insidious [7, 15, 40]. It usually manifests as a "slowly progressive febrile illness" [7]. Generally, the patients with TB pericarditis have weight loss, cough, dyspnea, orthopnea, chest pain, night sweats, fever, tachycardia, cardiomegaly, and pleural effusion [7, 23, 40, 51, 57]. The most frequent symptoms are cough, dyspnea, and fever [7, 40]. Chest pain is relatively seen less often [7, 43]. The patients usually have the symptoms of congestive heart failure without hypotension including sinus tachycardia, pulsus paradoxus (>12 mmHg), raised central venous pressure, palpable apical impulse, increased cardiac dullness, muffled heart sounds, pericardial friction rub, hepatomegaly, ascites, and peripheral edema [7, 15, 40, 43, 51, 57]. Right upper abdominal pain may be seen due to liver congestion [40]. Peripheral lymphadenopathy affecting the cervical glands has been reported [7]. Typical triad of acute pericarditis including chest pain, friction rub, and ECG changes are uncommon and seen in only 3–8% of the patients with TB pericarditis [43]. If pericardial fluid accumulation is quick or compensatory mechanisms are inadequate, hypotension and tamponade may occur [43]. Ten percent of patients with TB pericardial effusion have cardiac tamponade [40]. TB pericardial effusion is characterized by exudative nature that it contains high protein levels and an increased leukocyte count including mainly lymphocytes and monocytes and is frequently hemorrhagic [40]. There is no evidence of lung lesions in about half of the patients [23].

The underlying myocardium may be involved by inflammation of the pericardium. Elevated levels of biomarkers of myocardial damage (troponins, creatinine kinase, etc.), ECG changes related to myocardial injury, and impaired left ventricular systolic function may refer to the presence of myopericarditis [43].

12.2.2.2 Constrictive Pericarditis

Constrictive pericarditis occurs in 30–60% of the patients with TB pericardial effusion despite adequate treatment with antituberculous drugs and corticosteroids [9, 40]. It is considered one of the most important complications of TB. In developing countries, the most frequent cause of constrictive pericarditis is TB with a reported incidence of 38–83% [9]. The presence of tamponade at admission due to TB pericarditis is found to be correlated with development of subsequent constrictive pericarditis [57].

Parietal and visceral pericardia are thickened and fused as a result of fibrosis or fibrinous exudate induced by pericarditis [9]. This situation creates a rigid skin surrounding the heart which restricts diastolic filling of the ventricles and eventually decreases stroke volume of the heart as a result of Frank-Starling law. Inability of the ventricles to hold and pump enough volume of blood leads to congestive heart failure [9]. Long-standing constrictions may cause myocardial fibrosis and atrophy contributing heart failure and deteriorating the operative outcome [9].

The clinical picture may range from asymptomatic to severe constriction [40]. It may progress from an acute pericarditis to constriction phase passing through the effusion and absorption phases or may manifest as pericardial constriction without a history of acute pericarditis [9]. Pericardial knock, an early diastolic sound caused by rapid filling of the constricted left ventricle, and splitting of the second heart sound can be heard on auscultation. Low-voltage complexes and atrial fibrillation on ECG and enlarged cardiothoracic ratio on X-ray may be seen [40].

Although the TB pericarditis may have more aggressive clinical picture in immunocompromised patients, it has been reported that the incidence of constrictive pericarditis is significantly low in HIV-positive patients when compared to HIV-negative patients [9]. Because TB pericarditis and subsequent fibrosis and granuloma formation are mainly orchestrated by TH-1 cells, the presence of HIV infection decreases hypersensitivity reaction to the proteins of *M. tuberculosis* and the inflammatory process [9].

12.2.2.3 Effusive-Constrictive Pericarditis

Effusive-constrictive pericarditis (ECP) is a rare manifestation of TB caused by constriction of the visceral pericardium and compressive pericardial effusion [45]. It may occur during the continuum from pericardial effusion to constrictive pericarditis [45]. The prevalence of ECP is 4–4.5% [45]. The etiology is TB in 60% of all ECP cases [45]. Both effusion and visceral pericardial constriction increase pericardial pressure [40]. The treatment of ECP is difficult. Pericardiocentesis does not relieve pericardial pressure impairing the diastolic filling of the heart because fibrinous pericardial bands between thickened pericardial layers strictly loculate pericardial effusion preventing complete drainage of it [40, 45]. Also, pericardial pressure remains elevated after pericardiocentesis due to visceral constriction [40]. Elevated right atrial pressure persisting after pericardiocentesis despite intrapericardial pressure falling to near 0 mmHg is suggestive of ECP [45]. Similarly, the efficacy of

pericardiectomy in these patients is generally limited because removal of fibrinous exudate coating the visceral pericardium is almost impossible [40]. Visceral pericardiectomy may be performed in these patients to treat persistent heart failure [45]. Mortality rate is 4–50% [45].

12.2.3 Diagnosis

Chest radiography, ECG, and echocardiography are essential in the diagnosis and management of pericardial TB [43]. Chest X-ray shows an enlarged cardiac silhouette in more than 90% of cases [40]. It may also show radiological evidence of pulmonary TB and pleural effusions [7]. ECG changes including non-specific ST-T changes, QRS complex microvoltage, electrical alternans, and atrial fibrillation can be seen in patients with TB pericarditis [35, 40]. The presence of microvoltage on the ECG is usually related to pericardial effusion [40]. Echocardiography is an accurate and noninvasive method to diagnose pericardial effusion and constriction, but it is not suggestive about the etiology. Pericardial effusion with fibrinous strands between pericardial layers and pericardial thickening is frequently seen but not specific for TB pericarditis [7, 40, 51]. In constrictive pericarditis, thick fibrinous exudate in the pericardial sac or a thick skin surrounding the heart, which diminishes cardiac movements, is seen during echocardiography [40]. Also, CT scanning or MRI can be used to determine the presence of pericardial effusion, pericardial thickening, and mediastinal lymph nodes [7]. Mediastinal lymphadenopathy can be detected in almost all patients with TB pericarditis, and they regress or disappeared with antituberculous therapy which suggests TB etiology [7, 51]. The most frequently enlarged lymph nodes are the aortopulmonary (63%), paratracheal (52%), carinal (41%), pretracheal (26%), and hilar (15%) lymph nodes, respectively [7]. Nuclear imaging with gallium-67 and indium-111 scintigraphy can be used in the diagnosis of TB pericarditis, but its results do not reveal TB etiology [7]. Because proving the presence of TB in another organ in a patient with pericarditis is highly suggestive of the TB pericarditis, the presence of pulmonary or extracardiac TB should be explored with cultures and other techniques [7, 37]. Tuberculin skin test is not useful in diagnosis due to its high false-negative (25–33%) and false-positive (30–40%) results [37, 51, 57]. Negative test result does not exclude TB. But a strong positive test result should increase the suspicion of TB etiology [51]. Acid-fast bacilli should be searched in the sputum. It is positive in only 10–55% of the patients [40]. If the results of sputum and pericardial fluid examinations are inconclusive, gastric washings, urine culture, and right scalene lymph node biopsy may be used to identify the presence of acid-fast bacilli [7, 40].

The definitive diagnosis is mainly established by microbiological and pathological examination of the pericardial fluid and tissue to demonstrate TB bacilli or granulomas [7, 43]. Pericardiocentesis should be performed in all patients with suspected TB pericarditis [40]. Pericardial biopsy is generally recommended to obtain pericardial tissue sample [57]. Both procedures can be performed together by inferior pericardiotomy. This procedure also allows drainage of pericardial effusion for

treatment and prevents its reaccumulation [57]. Identification of *M. tuberculosis* in the pericardial fluid or tissue samples and identification of caseous granulomas in the tissue are required [37]. Culture of the pericardial fluid is more suggestive in the diagnosis of TB etiology than fluid smear and histology of the pericardium [7, 40, 51]. But isolating the organism or identification of caseous granulomas is often difficult. TB bacilli are detected in the pericardial fluid in only 0–42% of the patients by direct smear examination and in 53–75% by culture [40]. Also, it is not a timely method and may cause delays in diagnosis [57]. The diagnostic value of pericardial biopsy is about 10–64% [40, 51]. It provides positive results more frequently than pericardial fluid samples and should be performed [15, 57]. But it should be kept in mind that normal results obtained by the examination of pericardial fluid and tissue do not exclude TB pericarditis.

To improve diagnosis of TB pericarditis, a prediction model for endemic areas was suggested [51]. Scoring system has easily available five clinical and laboratory variables: 1 score for night sweats, 1 score for weight loss, 2 score for fever >38 °C, 3 score for white cell count $<10 \times 10^9$/L, and 3 score for serum globulin >40 g/L. It was shown that a total score of 6 or more in a patient with suspected pericarditis has a sensitivity of 86% and a specificity of 84% for the diagnosis of pericardial TB [51].

Traditional diagnostic tools are insufficient to diagnose pericardial TB [51]. Novel techniques including polymerase chain reaction (PCR) method to identify *M. tuberculosis*, enzyme-linked immunospot (ELISPOT) test detecting T cells specific for the *M. tuberculosis* antigen, adenosine deaminase activity (ADA), pericardial lysozyme, and interferon-γ concentration in TB pericardial effusion can be used [37, 40, 43, 51]. They provide rapid and accurate results for diagnosing pericardial TB. The genetic material belonging to *M. tuberculosis* bacilli is identified in pericardial fluid and tissue samples by PCR method [7]. Its diagnostic accuracy is close to conventional microbiological and pathological methods [7]. The sensitivity of the method is higher with tissue samples (80%) than with fluid (15%) [7, 40, 51]. Although it provides results more rapid than culture, high contamination rates and false-positive results (sensitivity 32%) make PCR unsuitable for daily clinical practice [7, 40, 51]. It was shown that elevated pericardial ADA (≥35 U/L) and interferon-γ levels (>200 pg/L) have high sensitivity (>90%) and specificity (>70%) rates for the diagnosis of TB pericarditis [7, 40]. ADA levels are associated with T-cell activity [7]. In a patient with high ADA level, bacterial pericarditis and neoplastic diseases should be excluded [51]. Interferon-γ is recommended as a more suggestive method [51].

12.2.4 Treatment

The treatment of TB pericarditis includes immediate combined drug therapy for different durations (6, 9, 12 months) [37, 38]. The goal of the treatment is both to treat the acute tamponade symptoms and to prevent the occurrence of constrictive pericarditis [57]. Antituberculous treatment increases survival significantly as shown by the mortality rates which has fallen from 80–90% in pre-antibiotic era to

8–17% in HIV-negative patients and 17–34% in HIV-positive patients currently but does not prevent the development of constrictive pericarditis [40]. A combined drug therapy consisting of rifampicin, isoniazid, pyrazinamide, and ethambutol for at least 2 months, followed by isoniazid and rifampicin lasting a total of 6 months, is suggested in extrapulmonary TB [40]. Steroids may be combined with antituberculous treatment to decrease mortality, the severity of symptoms, the rate of recurrence and rehospitalization, the incidence of constrictive pericarditis, and the need for pericardiocentesis or pericardiectomy [15, 37, 43]. But the adjunctive use of steroids is still controversial because they have been shown not to reduce mortality or need for pericardiectomy by some authors [15, 43, 57].

Open surgical drainage versus pericardiocentesis is another controversial issue in the treatment of TB pericarditis [57]. Early surgery including complete open drainage in TB pericarditis has been recommended by some authors to prevent repeated pericardiocentesis and development of chronic constrictive pericarditis [15, 38, 40, 57]. The presence of the opportunity to obtain pericardial biopsy during the procedure also favors open drainage [57]. In general, surgery is indicated in patients with pericardial effusion persisting despite medical treatment with or without repeated aspirations or with pericardial thickening and constriction [30]. The mortality rate in TB pericarditis may reach up to 85% in untreated patients [37]. It has been reported that average survival is 3.7 months in patients without specific treatment [7].

The treatment of constrictive pericarditis involves both antituberculous drugs for 6 months and pericardiectomy [40, 43]. There are some controversies about the timing of pericardiectomy. While some authors recommend immediate surgery for all patients with constrictive pericarditis, others recommend it for the patients in whom medical treatment fails [40]. But in latter recommendation, surgery should not be delayed if the patient has pericardial calcifications, a sequela of chronic disease [40]. Central venous pressure generally decreases on postoperative 2–4 days and returns to normal 4 weeks after surgery [9]. But about half of the patients have abnormal left ventricular diastolic filling after pericardiectomy, which is caused by myocardial fibrosis and atrophy or incomplete decortication [9]. Operative mortality of pericardiectomy is 3–16% and can reach up to 19% in patients with extensive calcification and adhesions [9, 40, 43]. Acute cardiac dilatation and failure may be seen following pericardiectomy, which is mainly arisen from the occurrence of myocardial atrophy [9]. Occurrence or worsening of mitral and tricuspid regurgitation after pericardiectomy due to ventricular dilatation or elongation of the papillary muscles can be observed [9].

12.3 Myocarditis

TB myocarditis was first reported by Maurocordat, a Turkish physician, in 1664 [35]. Although TB mainly involves the pericardium, the myocardium can rarely be affected [50]. The cause of higher affinity of *M. tuberculosis* to the pericardium rather than the myocardium is unclear [27]. Myocardial TB mostly occurs in an association with the pericardial disease [41]. Isolated TB myocarditis is extremely

rare with a prevalence of 0.2–2% [23, 41, 43, 50]. Involvement of coronary vessels and the endocardium by TB is exceedingly rare and usually associated with the infection located other parts of the heart [23, 50]. TB myocarditis is usually diagnosed postmortem with an incidence of <0.3% in all autopsies [35, 50, 54].

12.3.1 Pathology

The infection reach the myocardium via direct invasion from the pericardium or the pulmonary cavity, hematogenous spread, or retrograde lymphatic spread [35, 41, 43, 50]. The origin of the infection is pulmonary [35]. There are three types of involvement: (i) nodular tubercles (tuberculomas) characterized by central caseation, (ii) miliary tubercles resulting from hematogenous spread, and (iii) diffuse infiltration associated with tuberculous pericarditis rich in lymphocytes and giant cells [4, 12, 23, 27, 35, 41, 43]. Endocardial miliary tubercles, polyploid tubercles, tuberculous nodules on valves, and thrombi containing entrapped tubercle bacilli can be seen [23]. The most frequently affected heart chamber is left ventricle (68%). It can cause mitral and tricuspid insufficiency, but valvular stenosis and involvement of the semilunar valves are unusual [41].

12.3.2 Clinical Properties

The patients with TB myocarditis are usually asymptomatic [27, 41]. In contrast to pericarditis, myocarditis causes myocardial inflammation which can lead to serious complications including arrhythmias and heart failure [53]. Symptomatic patients may have atrial and ventricular tachyarrhythmias, ventricular fibrillation, conduction defects, long QT syndrome, congestive heart failure, dilated cardiomyopathy, ventricular aneurysms and pseudoaneurysms, superior vena caval obstruction, right ventricular obstruction, valvular dysfunction, coronary arteritis, and even sudden cardiac death [2, 4, 5, 13, 18, 21, 27, 33, 35, 41, 43, 54]. Accompanying pericardial involvement causing effusion, adhesions or constrictions complicates the symptoms of myocarditis [54]. The use of antituberculous drugs may cause arrhythmias including prolonged QT interval and torsade de pointes induced by isoniazid and moxifloxacin [35].

12.3.3 Diagnosis

The diagnosis of TB myocarditis is usually made at autopsy [41]. It should be suspected in patients with a history of TB exposure or from endemic areas presenting with nonischemic arrhythmias, congestive heart failure, or cardiogenic shock [27,

41, 42]. Cardiac MRI and late gadolinium enhancement have been reported to describe cardiac tuberculomas and myocardial infiltration [27]. If clinical suspicion is strong and imaging is suggestive for TB etiology, endomyocardial biopsy is indicated for early diagnosis [12, 27].

12.3.4 Treatment

The knowledge about the treatment of antemortem cases is limited and basically relies on empirical guidance [27]. The standard 4-drug antituberculous therapy is used to treat TB myocarditis and its complications [41, 43]. The duration of the therapy is unclear. Beta-blockers can be used to treat ventricular arrhythmias, but they have not been validated in this indication [27]. The efficacy of adjunctive steroids is also controversial [27].

12.4 Aortitis and Aneurysm

Mycotic aneurysm of the aorta secondary to TB infection was first described by Kamen in 1895 [8, 39, 60]. It is a very rare and life-threatening entity [3, 28, 36, 39, 49, 60]. The literature knowledge about the disease is mainly based on case reports [8, 39]. In the report of Parkhurst and Decker [48], TB aortic aneurysm was found in only 1 case (0.3%) among 338 aortic aneurysm cases detected in 22,792 autopsies between 1902 and 1951. This report belongs to a pre-antibiotic era, and it can be assumed that the incidence of aortic aneurysm secondary to TB infection is much less today due to the use of antituberculous drugs [20]. TB aortitis is seen 1% of the patients with latent TB [3]. The risk of aortitis and aneurysm is high in immunocompromised patients [36]. While case reports published in the pre-antibiotic era (before 1950) were mostly from autopsies, recent reports published in later years have shown that antemortem diagnosis and successful treatment of the disease have become possible due to enhanced imaging and surgical methods [8, 22].

12.4.1 Pathology

TB aortic aneurysms are seen in both abdominal and thoracic aorta with an equal frequency [3, 8, 36, 39, 43]. It can less frequently involve peripheral arteries including the subclavian, carotid, common iliac, hepatic, renal, femoral, and innominate arteries [3, 14, 16, 39]. TB infection reaches the aorta by means of two pathways: (i) commonly (in 75% of patients) direct invasion from an adjacent contagious lesion such as mediastinal lymphadenitis (63%), pulmonary lesions, empyema, pericarditis, spondylitis, or paravertebral abscess and (ii) rarely hematogenous or

lymphangitic spreading from primary lesions [8, 14, 16, 20, 22, 28, 32, 36, 39, 46, 47, 49, 60]. The descending aorta is more vulnerable to TB infection compared to the ascending aorta, which is represented by 46% of TB aortic aneurysms which are located at the descending aorta while only about 10% at the ascending aorta [8, 14, 28, 49]. This tendency may be explained by close proximity of the descending aorta to mediastinal lymph nodes [8, 14, 49]. Two specific groups of mediastinal lymph nodes located around the distal aortic arch and in the left pulmonary ligament are responsible for direct infection and aneurysm of the distal aortic arch and the supradiaphragmatic aorta [46]. Infrarenal segment is the most frequent involvement site of the abdominal aorta [36].

Aortic infection is associated with aortic stenosis, mycotic aneurysm, pseudoaneurysm, or autoimmune aortitis [8]. Four types of TB involvement in the arterial system were described: (i) miliary infection of the intima, (ii) tubercular polyps attached to the intima, (iii) infection of several layers of the arterial wall, and (iv) aneurysm formation [8, 22, 47]. Besides, a stenosing type of TB aortoarteritis was described recently [8]. It may occur as a consequence of hypersensitivity reaction to TB antigens [36]. Stenotic lesions involving the aorta (acquired coarctation) or renal artery can cause hypertension [43, 49]. Direct hematogenous spread may cause infection in the tunica intima of the aorta, but invasion via vasa vasorum or lymphatics may extend the infection to the tunica media or adventitia [22, 32, 36, 39, 47]. TB bacilli may also lodge in an atheromatous plaque, which alters the resistance of the vessel wall to infection, and spread through the aortic wall [8, 32, 36].

Infection of the aortic wall results in tissue destruction and necrosis [16, 39]. Destruction of the aortic wall is followed by its expansion to form a true aneurysm, named mycotic aneurysm. On the other hand, if necrosis involves the entire thickness of the aortic wall, it may be ruptured resulting in either massive bleeding or the formation of a perivascular hematoma [3, 16, 22]. Resorption of the encapsulated hematoma and communication of the residual cavity with the aortic lumen produce a false aneurysm, which is referred to as pseudoaneurysm [16, 39]. In contrast to true aneurysms, pseudoaneurysms lack all three layers of the arterial wall, which creates a tendency to aneurysm rupture and fatal bleeding, and are generally saccular in shape [60]. Typically, calcification is absent in all TB aortic aneurysms [8]. Most of the TB aneurysms are solitary, false, and saccular with a high risk for rupture and fatal bleeding [8, 14, 20, 22, 36]. Another typical presentation of vascular involvement in pulmonary TB is Rasmussen aneurysm that is a form of arteritis occurred at the vessels located near the cavitations and that causes recurrent hemoptysis in these patients [55, 60].

Atypical species of Mycobacteria including Bacille Calmette-Guerin (BCG), an attenuated strain of *Mycobacterium bovis* for adjuvant immunotherapy of bladder carcinoma or melanoma, and *Mycobacterium avium-intracellulare* (MAI) have also been reported to cause aortic aneurysms and pseudoaneurysms [3, 39].

12.4.2 Clinical Properties

Clinical presentation of the disease ranges from asymptomatic to rupture, bleeding, and shock. The age of the patients with TB aortic aneurysm ranges 6–86 years old (mean 50 ± 16 years) [36]. Both gender are involved equally [36]. The patients have fever, weight loss, pulsatile or palpable mass, chest pain, dysphagia, hoarseness, stridor, hemoptysis, intestinal bleeding, fistula, abdominal pain, or back pain regarding the localization of the aneurysm [8, 14, 16, 20, 22, 28, 43]. Patients usually presented in three clinical scenarios: (i) persistent chest, back, or abdominal pain, (ii) major bleeding or shock, or (iii) rapidly expanding palpable or pulsatile mass [36]. Rupture of the aneurysm is associated with the high mortality rate. Rupture into the esophagus, jejunum, stomach, pulmonary tree, peritoneal cavity, duodenum, and colon has been reported [3]. Acute aortic syndromes including aortic dissection may be seen [49]. Aneurysms of the ascending aorta may extend to the aortic root and the sinus of Valsalva and may cause aortic valve insufficiency and cardiac tamponade [43, 47]. The most frequent causes of death are rupture with massive bleeding, miliary TB, and congestive heart failure [36].

12.4.3 Diagnosis

The diagnosis is difficult and should be established as early as possible to prevent rupture and associated mortality [49]. Presence of active TB or past history is helpful in directing the clinician for this challenging diagnosis. CT and MRI are recommended to detect aortitis and aneurysm [16, 22, 36]. Thickening of the aortic wall may refer to aortitis without etiology [49]. MRI is more sensitive in this setting [49]. The presence of contrast extravasation during imaging indicates aneurysm rupture and is an indication for emergency surgery [43]. Aortography was the primary diagnostic tool previously, but it has been replaced by ultrasonography, CT, and MRI which can easily detect the aneurysm by a noninvasive manner [16, 20]. Also, TB aneurysms may not have fill defect in angiography [36].

The definitive diagnosis can ultimately be established by histological examination of surgical specimens revealing granulomatous aortitis with caseous necrosis and positive acid fast bacilli on Ziehl-Neelsen staining [49]. Negative test results do not exclude the diagnosis of TB etiology.

12.4.4 Treatment

Neither medical nor surgical treatment alone is sufficient for a complete cure. Optimal therapy is the combination of both preoperative and postoperative antituberculous drugs and operative methods [8, 14, 16, 20, 22, 32, 36]. Once TB

aneurysm has been diagnosed, 4-drug treatment should immediately be started to cover the postoperative period, and the operation should be performed urgently [8, 14, 22, 36, 47]. The duration of antituberculous therapy is controversial, but it should be extended to at least 9–12 months in patients with severe systemic infection [3]. Some authors recommend lifelong antibiotic treatment after prosthetic graft implantation [3]. Prolonged antibiotic treatment should be preferred in patients with an extra-anatomic bypass to prevent blowout of the aortic stump due to recurrent infection [3].

Surgical options include extra-anatomic bypasses, in situ insertion of aortic conduits, patch closure or direct closure of the aortic rent, and endovascular aneurysm repair [3, 8, 22, 60]. The size of the aneurysm is not a limitation for the need of surgery, because even a small pseudoaneurysm down to 1 cm in diameter can rupture and cause fatal bleeding [22, 36]. Resection of the infected aortic segment with surrounding tissues and revascularization of the lower body with arterial reconstruction is the frequently performed procedure in such cases [20, 32, 60]. The extent of aortic wall resection should be decided with visual inspection rather than time-consuming frozen section and histologic study to shorten cross-clamp-related ischemia time [8, 22]. Insufficient resection of the rent margin which contains infective material is associated with recurrence [8]. The type of aortic repair is chosen according to the rent size: An interposition graft should be inserted in the presence of a large rent; otherwise a patch repair may be performed [8]. Usually, an interposition graft is required to reconstruct a true aneurysm, but patch or direct closure can be performed in pseudoaneurysms [20]. In the presence of active infection or abscess formation, complete resection of the aneurysm and extended removal of the infected tissue should be followed by an extra-anatomic bypass to keep prosthetic material away from the infection area [20]. Recurrence of aneurysm and graft infection can occur [60]. Preoperative antituberculous drugs and adjunctive procedures such as drainage of paraspinal abscess and antibiotic-soaked grafts may be helpful to prevent persistence or recurrence of the infection [10, 16, 20]. Close postoperative follow-up is required to detect recurrence [20, 22]. Mortality of the surgery is 14–20% and reaches up to 50% in emergent operations [3, 60]. Causes of perioperative mortality are massive gastrointestinal hemorrhage, aorto-enteric fistula, renal failure, rupture of another tuberculous aneurysm, and acute heart failure [16].

Currently, endovascular treatment of TB aneurysms is increasingly preferred method [14]. Debridement and removal of the infected tissue which is the main part of surgical success are impossible in the endovascular treatment [14]. In the presence of persistent infection, the efficacy of drug therapy decreases, and the risk of rupture and fatal bleeding increases [14]. For that reason, careful patient selection is the key element for the success of the treatment with stent-graft deployment [10]. The placement of intravascular prosthesis to treat TB aneurysms has been reported having a high risk of infection recurrence and bleeding [39]. Patients who are relatively sterile during the procedure have better results and lower long-term complications [10]. Also, endovascular treatment can be considered as a bridge to surgery or as a palliative destination therapy [32].

12.5 Takayasu Arteritis

Takayasu arteritis (TA) is a rare, large-vessel vasculitis of unknown etiology that primarily involves the aorta and its major branches including subclavian and carotid arteries. It is primarily an inflammatory disease causing chronic and progressive vessel wall inflammation which is responsible from concentric thickening of the vessel wall producing arterial stenosis with ischemic complications or aneurysm formation [26]. Clinical manifestations of TA are related to systemic inflammation and the site of vascular lesions. While systemic inflammation causes constitutional symptoms including fever, malaise, night sweats, anorexia, arthralgia, and lymphadenopathy, vascular complications include pulse defects, claudication, dizziness, visual disturbances, bruits, and blood pressure difference between the arms [34].

An association between TB and TA has been suggested for more than a half of century [19, 55, 58, 59]. There is a clinical correlation between two clinical entities without a proven causative mechanism [26]. The prevalence of TB is higher in patients with TA in comparison with the general population [19, 34, 59]. Case series from Asia, South America, and Africa have revealed that the frequency of TB in patients with TA ranged between 22 and 70%, while TB rates were 0.03–1.5% in the general population in these regions [19, 59]. Purified protein derivative (PPD) is positive in 81–100% of the patients with TA but 66% in normal controls [6, 59]. Also, hypersensitivity reaction to specific antigens of *M. kansasii* (84% vs 11%) and *M. avium* (78% vs 15%) is more frequently positive in TA than non-TA patients [6]. Active TA is more frequent in patients with TB lymphadenitis (21% in TA vs 1% in pulmonary TB) than with pulmonary TB [34]. TB lymphadenitis in para-aortic or mesenteric lymph nodes closely located to inflamed vessels in TA has been frequently reported [34]. PPD with induration over 10 mm is also more frequent (92.5% vs 89%) in TA patients with extrapulmonary TB [6]. Clinical and angiographic features of TA in patients with and without TB are indistinguishable [34]. Histopathological features of TA are similar to those of TB lesions including granulomatous inflammation and Langerhans-type giant cells [1, 24]. Gene sequences associated with *M. tuberculosis* including IS6110 and HupB genes were found within tissues of the aorta from patients with TA, which implies the relationship between arteritis and latent infection [55]. Demonstration of tubercular lymph nodes in the vicinity of arterial lesions and increased levels of agalactosyl IgG may also represent the association between TB and TA [1].

On the other hand, the use of anti-TNF therapy providing remission in TA patients is not associated with the occurrence of mycobacterial infections, which is reasonable to infer that if TA results from active or latent TB infection, anti-TNF agents should aggravate clinically evident TB [6]. Quantiferon-TB Gold test, which detects TB infection by measuring in vitro T-cell interferon-gamma release in response to antigens highly specific for *M. tuberculosis*, was shown to have similar positive results in TA and the controls indicating that the rate of TB infection in TA patients is not higher than the general population [24]. Any genetic relationship between TB (both pulmonary and extrapulmonary) and TA regarding HLA-B alleles

did not detected [56]. In patients with concomitant TA and TB, TB does not affect the clinical course of TA [34].

In TA, inflammation characterized by mononuclear (lymphocytes, macrophages, plasma cells, and giant cells) infiltration begins around the vasa vasorum at the medio-adventitial junction and involves the entire adventitial layer and outer third of medial layer [29, 55, 58]. The intimae remain normal until fibrosis involves it [55]. Granulomatous reaction with giant cells, laminar necrosis, fragmentation of elastic fibers, and loss of smooth muscle cells can be seen [58]. There is reactive fibrosis, medial scarring, and vascularization [58]. In the healing stage, fibrosis involves all three layers of the vessel [58]. Histopathological changes including intimal and adventitial fibrosis and medial degeneration resulted in stenosis or aneurysm formation [29]. The etiopathogenesis of the disease is still unknown, but an autoimmune basis related to genetic, infectious, or environmental factors is strongly suggested [58]. There is clinical relationship between TA and TB. In spite of this association, the exact link between TB and TA cannot be demonstrated until now.

It has been widely suggested that antigens of *M. tuberculosis* may stimulate T cells to produce autoimmune reaction against the vascular wall resulting in the onset of TA [6, 26, 59]. A significant increase in antibody titers against the proteins of TB bacilli including 65 kDa heat-shock protein (HSP65) has been found in patients with TA [19, 59]. HSP65 is the most frequently emphasized protein in this setting. Heat-shock proteins are found in a wide range of species extending from bacteria to humans and constitute an ancient intracellular self-defense system with scavenger activities to protect cellular proteins from denaturation [1, 6, 52]. They are expressed as a result of cellular stress including infections, increased blood pressure, overload of endoplasmic reticulum, oxidation/reduction imbalance, mechanical stress, and inflammation [6, 52]. It was shown that human 60 kDa heat-shock protein (HSP60) is homolog to HSP65, and both TA and pulmonary TB patients have higher prevalence of antibodies IgG isotype reactive to both HSP60 and HSP65 [1, 6]. These antibodies may have a cross-reaction with self-antigens of human vessels leading an autoimmune vessel damage and vascular disease [1, 6, 19, 29, 34, 59]. Not only in TA, HSP65 has been implicated in various rheumatic diseases in humans [1].

Another proposed mechanism is the increased levels of agalactosyl IgG which is markedly elevated in both mycobacterial disease and several autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease, and TA [59]. In addition, proinflammatory cytokines, including interleukin-18 and TNF-α, contributing immunity against TB infection and granuloma formation may contribute to pathogenesis of TA, because interleukin-18 and TNF-α are upregulated in patients with TA [59]. Although *M. tuberculosis* has never been demonstrated directly in the arterial tissues of patients with active or inactive arteritis [6], the presence of IS6110 and HupB gene sequences of *M. tuberculosis* in the aortic tissues of TA patients implies that TB may directly induce inflammatory reaction in TA without an autoimmune mechanism [34, 55]. Also, BCG vaccination was proposed for the etiology of TA [6, 29].

12.6 Atherosclerosis

Atherosclerosis is the main pathology of cardiovascular diseases which are responsible for one third of all deaths in the world according to the World Health Organization (WHO). Although there is no clinical evidence for increased atherosclerosis development in TB [52], it was shown that patients with pulmonary or extrapulmonary TB had a 40% increased risk for acute myocardial infarction and unstable angina pectoris and a 50% increased risk for ischemic stroke [19]. The relationship between TB and atherosclerosis is unclear, but it should be considered that some mechanisms seen in the course of TB may potentially be related to the occurrence or progression of atherosclerosis.

A connection between hardly growing intracellular organisms (cytomegalovirus, Herpes simplex virus, Chlamydia pneumoniae, and Helicobacter pylori) and atherosclerosis has been implicated due to their chronic or latent infection habit that may cause persistent inflammation leading to atherosclerotic plaque formation [19, 52]. Atherosclerosis is primarily an inflammatory disease. Activated leukocytes including T lymphocytes and macrophages and inflammatory markers including C-reactive protein, fibrinogen, serum amyloid, interleukins, TNF-α, and adhesion molecules are related to the progress of atherosclerosis [52]. *M. tuberculosis* has similar features with microorganisms which are accused of leading atherosclerosis and similarly induces chronic inflammation which may have a role in atherosclerosis.

Cross-reaction of antibodies to heat-shock proteins may be associated with atherosclerosis, because the endothelial cells express them when they are activated by various stressors [19, 61]. A significant correlation between anti-HSP65 antibodies and carotid atherosclerosis has been reported [19]. Patients with atherosclerosis have higher titers of antibodies against heat-shock proteins [52, 61]. Also, it was found that there are T cells specifically responding to heat-shock proteins in atherosclerotic plaques [61]. As mentioned above, antibodies produced against *M. tuberculosis* HSP65 can induce a self-reaction of T and B cells against human HSP60 through molecular mimicry which may play a role in the development of atherosclerosis [52]. The anti-HSP60 titers in the animals immunized with BCG vaccine were found to be correlated with atherosclerotic plaque formation [52].

TB induces free radical production such as reactive nitrogen intermediates (RNI) and reactive oxygen species (ROS), which enhance oxidative stress and decrease antioxidant activity in patients [17, 44]. Oxidation/reduction imbalance is associated with LDL oxidation which has a central role in the pathogenesis of atherosclerosis via endothelial dysfunction, expression of the adhesion molecules, and foam cell formation. Oxidation/reduction imbalance in TB patients may be associated with an enhanced susceptibility of LDL to oxidation predisposing TB patients to a higher risk of atherosclerosis [44].

12.7 Deep Vein Thrombosis

There are several classic risk factors for venous thromboembolism (VTE), and infection is considered one of them. Also, TB is an independent risk factor for VTE. Inflammation, stasis, and hypercoagulable state which occurred during the course of TB infection can cause VTE [25, 31]. In the report of Dentan et al. [11] involving the data of 33.048.852 in-patient and outpatient admissions, an association between pulmonary TB and VTE without underlying coagulation disorders was established. The prevalence of VTE in patients with TB is 2–4% [11, 25]. The risk of VTE in TB patients represented by odds ratio (OR) is close to that of neoplasia (1.55 vs 1.62) which is a well-known risk factor for VTE [11]. TB can produce a hypercoagulable state attributed to increased platelet aggregation; thrombocytosis; increased fibrinogen, factor VIII, plasminogen activator inhibitor 1 plasma, and antiphospholipid antibody levels; and decreased antithrombin III and protein C levels [11, 25, 31]. Besides, venous compression by retroperitoneal lymph nodes may cause stasis and thrombosis [11, 31]. Endothelial injury caused by TB bacilli and inflammation or the use of rifampin may take part in the pathogenesis of VTE [25]. In addition to deep vein thrombosis and pulmonary embolism, thrombosis of unusual sites including cerebral venous sinuses or hepatic vein has been reported in patients with pulmonary TB [25].

Hypercoagulable state is recovered following commencing antituberculous therapy [31]. The treatment of VTE in TB patients should include both anticoagulation and antituberculous therapies [25]. The maintenance of target INR level may be difficult, and a high dose of warfarin may be required due to hypercoagulable state induced by rifampicin, which is a cytochrome p450 inducer and increases clearance of anticoagulants [31].

VTE is an independent prognostic factor for TB patients and independently associated with mortality (OR = 3.87) [11]. Mortality is higher in patients with both TB and VTE (15%) than in patients with TB (2.7%) or VTE (2.5%) alone [11].

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Chapter 13
Cutaneous Tuberculosis

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Tuberculosis, an infection caused by *Mycobacterium tuberculosis* bacilli, has existed for millennia, and till today it continues to be a major global public health concern. WHO estimates that 20–40% of the world population is affected and that in 2015 alone there were 10.4 million new TB cases (including 1.2 million among HIV-positive people), of which 5.9 million were among men, 3.5 million among women, and 1.0 million among children. Overall, 90% of cases were adults and 10% children, and the male/female ratio was 1.6:1. The bulk of the disease globally is pulmonary TB, but the bacilli can affect any other body organ including the skin in the form of extrapulmonary TB in about 8.4–13.7%. This makes tuberculosis of the skin a relatively uncommon infectious disease comprising only 1–2% of the extra-pulmonary tuberculosis cases and approximately 0.1–1% of all cutaneous disorders [1]. Only 5–10% of infections with *M. tuberculosis* lead to disease, highlighting the low virulence of the organism. Cutaneous tuberculosis increases with concomitant infection with HIV, an increase in multidrug-resistant TB and the recent rise in the therapeutic use of biologics specifically antitumor necrosis factor (Anti-TNF) [2].

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13.1 Classification

The clinical presentation depends mainly on the route of infection, cellular immunity, and virulence of the infecting organism. A variety of local factors play a role as well such as interrupted skin barrier, vascularity, lymphatic drainage, and the proximity to the regional lymph glands [3]. There are numerous presentations and morphologies that are classified based on the mode of infection and immunologic status of the host. Cutaneous TB is classified into three main categories:

1. Exogenous inoculation
2. Endogenous infection
3. Hematogenous spread

13.1.1 Exogenous Inoculation

Tuberculous chancre is the resulting lesion from autoinoculation into the skin or mucous membrane of a patient with no prior exposure or immunity to *Mycobacterium tuberculosis*. Introduction of the bacteria into the skin may result from interruption of the skin barrier resulting from skin or mucous membrane injury such as wounds, tattoos, piercings, tooth extraction, ritual circumcision, and mouth-to-mouth resuscitation [4]. It commonly appears on the face and limbs of children. The tuberculous chancre presents with a painless non-healing papule or ulcer that may enlarge to a size of 5 cm [5], typically 2–4 weeks after inoculation. The ulcer is shallow with undermined edges and granular or hemorrhagic base. Regional lymphadenopathy develops in 3–8 weeks. The development of a cold abscess may occur weeks to months later that may perforate resulting in sinus formation. If untreated, the lesion may last up to a year and eventually heal leaving a scar. The regional lymph nodes slowly subside and may calcify in 50% of the cases [5].

Reactivation of the disease or hematogenous spread may occur if the immune response was inadequate.

Mucous membrane lesions may present as conjunctival edema or ulceration with regional lymphadenitis [6]. Oral lesions, although rare, have been reported [7].

In the early phase, the histopathology of the lesion shows a mixed dermal inflammatory infiltrate and an abundance of acid-fast bacilli. After a 3–6-week period, a tuberculoid granuloma develops in the lesion and regional lymph node and may be accompanied by caseation necrosis [8].

Tuberculosis verrucosa cutis (warty tuberculosis) occurs in individuals with a moderate to high immunity on re-exposure or inoculation. It commonly presents on the hands in adults or lower extremities in children. It usually starts as a painful firm papule with a purple inflammatory halo. The lesion, usually solitary, grows slowly into an asymptomatic hyperkeratotic verrucous plaque. Irregular extension of the edges leads to a serpiginous appearance [9]. If untreated the lesion grows very slowly for many years. Occasionally, spontaneous resolution occurs leaving an atrophic scar.

Histopathology of such lesions shows marked hyperkeratosis and hyperplasia of pseudoepitheliomatous proportions of the epidermis accompanied by caseating granulomas in the dermis. Acid-fast bacilli can be seen if the specimen is carefully examined [5, 8].

13.1.2 Endogenous Infection

This results from involvement of the skin as direct extension from an underlying focus of infection such as subcutaneous tissue, lymph gland, lacrimal gland or duct, or bones and joints.

Scrofuloderma is reported as the commonest form of cutaneous tuberculosis in children under the age of 10 years [10]. Overlying the infected focus, a red-blue, mobile, firm, asymptomatic nodule develops. Subsequent liquefaction and breakdown may take months and form ulcers and sinuses. Ulcers may follow a linear or serpiginous pattern with bluish undermined edges and granulation tissue at the base [9]. Scarring and granulation tissue may give rise to irregular fungating tumors.

Histopathology shows caseation necrosis at the center with tuberculous granulomas at the periphery of the lesion. Acid-fast bacilli can usually be isolated from the necrotic debris.

Orificial tuberculosis (tuberculosis cutis orificialis) autoinoculation of the mucous membranes or skin adjacent to orifices with large number of viable tubercle bacilli in patients with advanced infection of pulmonary, intestinal, genital, or urinary systems. These patients are severely ill and have low immunity. The lesions, commonly in the oral mucosa, are red painful nodules that quickly form shallow ulcers with bluish edges that fail to heal [9].

13.1.3 Hematogenous Tuberculosis

Infection of the skin through hematogenous dissemination or lymphatic seeding is referred to as hematogenous tuberculosis. Lupus vulgaris is the commonest form of hematogenous spread and occurs in individuals with moderate to high degree of immunity [4]. It may also occur as a result of inoculation, BCG vaccination, direct extension, or lymphatic spread. Over 80% of the lesions are located on the head and neck, especially around the nose [9]. A reddish-brown plaque is the initial presentation with the characteristic apple-jelly appearance on diascopy. The lesion slowly increases in size and becomes firm, elevated, and brown in color. There are five main clinical presentations. The plaque form, most common, is red-brown in color and may have a smooth or psoriasiform surface with irregular edges that become hyperkeratotic. Variable scarring occurs in these lesions. Ulcerating and mutilating form is destructive and invades deep tissue and cartilage leaving necrosis

crusts and scars. The vegetative form is characterized again with ulceration and necrosis but with minimal scarring. It is disfiguring especially when nasal or auricular cartilage is invaded. Tumorlike forms, either smooth or hyperkeratotic, commonly involve the earlobe and may cause lymphedema and vascular dilatation. Papular and nodular form present as multiple lesions after temporary immunosuppression.

A skin biopsy shows tuberculoid granulomas with lymphocytes at the periphery in the upper and mid dermis. Occasional central caseation is demonstrated. Lesions are paucibacillary, but acid-fast bacilli can be seen in some sections [8].

Tuberculous gumma also known as metastatic tuberculous abscess is a rare form of hematogenous dissemination in hosts with low immunity and results in single or multiple cutaneous or subcutaneous lesions. Abscesses are generally non-tender and may present as a fluctuant abscess nodule or firm subcutaneous nodule [9]. The overlying skin will eventually breakdown and result in ulcers and sinuses. Tubercle bacilli can be isolated from the discharge [5, 9].

Miliary tuberculosis (tuberculosis cutis miliaris disseminata) is a rare life-threatening form and commonly affects young children and patients with immunosuppression. Multiple bluish to red-brown papules, vesicles, and hemorrhagic lesions initially appear. The vesicles later become necrotic and ulcerate. Histopathology shows a chronic non-specific inflammatory infiltrate in the dermis surrounding a necrosis and abscess formation with abundance of acid-fast bacilli.

Tuberculids, initially described by Darier in 1896, result from a hypersensitivity to tuberculous organisms or its products in individuals with high immunity. They characteristically have a positive tuberculin test, a positive response to anti-tuberculous therapy and difficulty in isolating the organism.

True tuberculids can be classified into three main categories:

1. Micropapular: lichen scrofulosorum
2. Papular: papulonecrotic tuberculid
3. Nodular: erythema induratum of basin, nodular tuberculid

Lichen scrofulosorum is an uncommon lichenoid eruption presenting in children and young adults. A crop of asymptomatic skin-colored, yellowish, or reddish-brown lichenoid papules commonly appear on the trunk and proximal extremities. Histopathology of the involved skin shows perifollicular noncaseating tuberculoid granulomas. AFB are not demonstrable [8].

Papulonecrotic tuberculids present as dusky red necrotic papules mainly on the extremities of young adults. The lesions heal with a varioliform scar. Histopathology of the lesion shows ulceration involving the epidermis and variable thickness of the dermis with area of necrosis. A palisade of histiocytes can be seen surrounding the lesion. Vasculitis, fibrinoid necrosis, or thrombosis can be seen in adjacent vessels.

The lesions of erythema induratum of Bazin are localized to the subcutaneous fat and present with ill-defined nodules commonly located on the posterior aspect of the lower legs. The lesions may ulcerate and yield shallow ulcers with irregular bluish edges. It is a lobular panniculitis with neutrophilic vasculitis.

13.2 Non-tuberculous Mycobacteria

Infections with atypical mycobacteria, as they were previously named, occur predominantly in immunocompromised hosts. In immunocompetent hosts, infection follows skin penetration and is usually localized, while there is a tendency for dissemination in immunocompromised patients. There are many species in this category, but the commonest organisms causing cutaneous disease are members of the *M. fortuitum* complex (*M. fortuitum*, *M. chelonae*, and *M. abscessus*), *M. marinum*, *M. haemophilum*, and *M. ulcerans*. These organisms are widely distributed in the environment and can be found in soil, water, flora, commensal organisms of the skin, and some fauna [4, 5].

M. fortuitum complex species are fast-growing mycobacteria capable of causing disease in both immunocompetent and immunocompromised hosts. In the former, there is a history of trauma resulting in a localized disease, while in the latter it causes disseminated disease with no history of penetrating injury. Localized disease may present as nodules, abscesses, ulcers, cellulitis, and sinuses. Disseminated cutaneous disease presents with multiple nodules with no specific pattern.

Fish tank granuloma or swimming pool granuloma is the cutaneous disease caused by inoculation with *M. marinum*. It is isolated from both salt water and freshwater. Incubation period can be as early as 2–3 weeks or as late as 9 months. Lesions start as nodule or pustule that may later form an ulcer or abscess and eventually a verrucous plaque. Lesions are usually multiple and may extend in a sporotrichoid pattern along lymphatic drainage.

Buruli ulcer is the local name given to the cutaneous disease caused by *M. ulcerans* when it was first described in 1897 in Uganda [9]. It has since been reported mainly in tropical and subtropical riverine areas. Mode of transmission is not known yet. Most patients are children under the age of 15 years. They present with a firm mobile subcutaneous nodule that breakdown into a painless shallow necrotic ulcer with undermined necrotic edges. Ulcers are usually single but grow over weeks to several centimeters in size.

The natural habitat and mode of transmission of *Mycobacterium haemophilum* is not known. It affects immunocompromised individuals especially organ transplant recipients and patients on long-term immunosuppression. Patients present with multiple painful, violaceous nodules on the extremities that develop into ulcers or abscesses. Systemic symptoms may accompany cutaneous disease such as weight loss, tenosynovitis, osteomyelitis, joint effusions, or respiratory tract symptoms [9].

13.3 Treatment

The current therapeutic options for cutaneous TB are limited to the conventional anti-tuberculous drugs in addition to some surgical interventions in certain indications (surgical excision of lesions and correction of deformities). The standard

therapeutic agents used include the combination of isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. It is important to note that most of the reported cases of cutaneous TB are sensitive to the commonly used agents and resistant cutaneous TB is very unusual. The treatment of cutaneous tuberculosis is similar to that of pulmonary TB, where a combination of anti-tuberculous agents are used in two phases: intensive or bactericidal phase using the combination of isoniazid, rifampicin, ethambutol, and pyrazinamide for 8 weeks and the maintenance or sterilizing phase for 16 weeks with isoniazid and rifampicin. In cutaneous TB cases in HIV-positive patients, the maintenance phase of the treatment is extended from 16 to 28 weeks. If the cutaneous TB lesions are close to natural orifices, we can use lactic acid 2% and local anesthetic agent.

For cutaneous infections with atypical mycobacterium, the anti-TB drugs are less effective, and hence a variety of antibiotics could be used to treat such infections depending on sensitivity profile. The therapy in such cases is usually difficult and requires prolonged duration. To date there are no topical anti-TB drugs that are available for use in cutaneous tuberculosis [4].

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Chapter 14
Ocular Tuberculosis

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Tuberculosis is an airborne communicable disease caused by the acid-fast bacillus (AFB) *Mycobacterium tuberculosis* and most commonly involves the lungs. It can also affect any other part of the body and remains the most common single cause of morbidity and mortality worldwide [1].

Periocular or intraocular infection mainly by *Mycobacterium tuberculosis* or by *Mycobacterium bovis*, *Mycobacterium africanum*, and *Mycobacterium microti* is defined as "ocular tuberculosis" (ocular TB) [2].

Primary ocular tuberculosis is the ocular disease without systemic involvement or in which the eye is the entry of the mycobacterium into the body, and secondary ocular TB is ocular involvement as a result of hematogenous spread from a distant organ or direct invasion from adjacent tissues, like the sinus or cranial cavity.

Although it is estimated that 1.4% of patients with pulmonary TB will eventually develop ocular disease, ocular TB may not be associated with clinical evidence of pulmonary TB [3]. Also, nearly 60% of patients with evidence of extrapulmonary TB may not have evidence of pulmonary TB [1].

The most common clinical presentation of ocular tuberculosis is uveitis while posterior uveitis being the most common followed by anterior uveitis, panuveitis, and intermediate uveitis [4].

In the nineteenth century, TB was considered as the common cause of uveitis. In the 1940s, Guyton and Woods placed TB as the cause of 80% of all granulomatous uveitis [5]. However, with new diagnostic tests, diagnostic criteria for ocular tuberculosis have become more strict, and previously undefined causes like sarcoid, toxoplasmosis, and histoplasmosis were defined; the number of uveitis cases attributed to *M. tuberculosis* declined [5]. Since the 1980s, reports in the literature cite tuberculosis (TB) as an etiology of uveitis from 0 to 4% [5–9]. The region-specific

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prevalence for presumed ocular tuberculosis is reported as 0.4–9.8% for India, 4% for China, and 7% for Japan [10–13].

TB is reported as a prominent cause for chronic iridocyclitis, disseminated choroiditis, and periphlebitis in Denmark and for posterior uveitis in Russia [14, 15].

Singh et al., in their study with PCR, defined intraocular fluid and reported that 30% of the patients with uveitis had infectious origin, the two thirds being intraocular TB [12].

TB is defined as etiological factor in 0.3% of the uveitis patients in the tertiary centers in Turkey [16].

14.1 Signs and Symptoms

Blurred vision, photophobia, and redness of the eye are the most common symptoms. However patients may also be asymptomatic or have complaints like headache, flashes, and floaters.

14.2 Clinical Manifestations of Ocular TB

Ocular TB is a hematogenous dissemination of the pulmonary and extrapulmonary TB, and primary ocular infection through conjunctiva may rarely be seen in children. Symptomatic disease is usually due to reactivation of silent lesions in the ocular tissues rather than primary infection.

The presence of eye lesions due to *M. tuberculosis* antigen hypersensitivity from a distant focus like the lungs, without the presence of bacillus in the eye, is another form of ocular TB [1].

Ocular TB is usually unilateral and asymmetric. It may affect ocular surface, eyelid, conjunctiva, cornea, sclera, uvea, choroid, retina, orbital, lacrimal gland, and optic nerve extending to the central nerve system [5, 17].

14.3 Major Clinical Manifestations

1. *Uveitis* is the most prominent clinical manifestation of the ocular TB predominantly posterior uveitis, followed by anterior uveitis, panuveitis, and intermediate uveitis. It has a variety of uveitis presentations making the TB an important masquerading, in uveitis patients.

   Posterior uveitis with disseminated choroiditis is the most common manifestation of tuberculous uveitis and is often bilateral [18]. Multiple, discrete, yellow lesions uni- or bilaterally may be seen in the posterior pole in wide range of diameters in size (choroidal tuberculoma). As lesions progress, their borders

may become more distinct, and the center becomes paler leading to an atrophic scar. Subretinal neovascularization, subretinal abscess, and choroiditis may later develop.

Acute or chronic granulomatous anterior uveitis may be seen with mutton-fat keratic precipitates, iris or angle granulomas, posterior synechiae, hypopyon, secondary cataract, vitritis, and secondary glaucoma [19]. Intermediate uveitis is seen with pars planitis like signs as snow banking, low-grade chronic vitritis, peripheral vascular sheathing, and peripheral retinochoroidal granulomas [19].

Disc edema, periphlebitis, vasculitis, and vitritis may be present.

2. *Retinitis and Retinal Vasculitis*

   Retinal manifestation is usually due to choroidal manifestation. Retinal vasculitis mostly is in the retinal veins with perivascular cuffing; arteries may rarely be associated.

3. *Optic Neuropathy and Neuroretinitis*

   Optic neuropathy may be the result of the direct invasion of the microorganism or hypersensitivity to the microorganism. Optic neuritis, papillitis, papilledema, retrobulbar neuritis, and neuroretinitis may be other manifestations [19–22].

4. *Endophthalmitis and Panophthalmitis*

   This form is acute and progressive, leading the hypopyon fill the anterior chamber and vitreous cavity. Subretinal abscess may occur, and liquefaction necrosis may result in perforation of the globe [19].

5. *Choroidal Tubercles*

   These lesions are the most recognized lesions in intraocular TB and are an indicator of hematogenous spread of the mycobacteria.

   Choroidal tubercles are unilateral, yellowish lesions with poorly defined borders and typically elevated centrally, ranging from 1–4 to several optic disc sizes in diameter, usually less than five in number and may become more pigmented as time passes. Tubercles near or at macula present with diminished visual acuity otherwise may be asymptomatic.

   In an autopsy series, choroidal tubercles are found in nearly 50% of the cases [23].

6. *Orbital involvement* occurs most commonly in children, although rare cases have been reported in adults. Findings may include a draining sinus tract with/or radiographic evidence of bony destruction.

7. *Tuberculous conjunctivitis* has been reported in the literature: usually unilateral, chronic conjunctivitis, occasionally associated with an ulcer, subconjunctival nodule, pedunculated polyp, or conjunctival mass or ulceration. Most do not have systemic manifestations of TB and may represent primary ocular tuberculosis.

8. *Eyelid involvement:* Tuberculosis can also present as an eyelid abscess or chalazion-like mass. Spontaneous drainage of abscess can form draining sinus tract.

9. *Lacrimal gland involvement* (dacryoadenitis) may be indistinguishable clinically from bacterial infection.
10. *Scleritis:* Scleral involvement, although rare, may also apply. There are biopsy-proven cases of TB scleritis.
11. *Phlyctenulosis* is a type IV hypersensitivity reaction that presents as an inflammatory mass on the cornea and can be associated with *Staphylococcus aureus* as well as tuberculosis.
12. *Eales' disease.* This is a rare disorder that is not associated with *M. tuberculosis* specifically but with a positive tuberculin skin test. It is characterized by recurrent vitreous hemorrhages in young men.

14.4 Diagnosis

The diagnosis of ocular TB is often problematic due to the masquerading nature of the disease and it is impractical to obtain biopsy for culture and direct visualization of the microorganism to provide definitive proof of ocular TB [24]. Definitive diagnosis may be achieved by examination of smears and staining for acid-fast organisms, cultures of intraocular tissue/fluid for *Mycobacterium tuberculosis.* Historically, the only way to prove the ocular TB was enucleating the eye for histopathological evaluation. Recently obtaining intraocular specimens via pars plana vitrectomy or chorioretinal biopsy makes it possible to obtain a histopathological diagnosis while keeping the eye intact. However, usually the bacillus obtained from the intraocular fluids is low in number making it difficult to diagnose the microorganism by direct microscopy and culture test. However smears from lesions with caseification necrosis or endophthalmitis may show acid-resistant dye positivity for the bacillus [19]. Due to amount limitations of the intraocular fluid, PCR became an important diagnostic tool by requiring small amounts of specimen. Anterior chamber fluid; vitreous, subretinal fluid; and rarely chorioretinal biopsy specimens or epiretinal membrane obtained by vitrectomy may be analyzed by PCR [19].

When it is impossible to get a specimen by surgery, it is important to evaluate the chest X-ray for infiltration, cavitation, or pleural effusion. Acid-fast stains and cultures can be performed from urine, spinal fluid, or sputum.

14.5 Diagnostic Criteria for Ocular TB

Although there are not well-defined criteria for ocular TB, the guidelines for ocular tuberculosis reported in several studies in the literature were presence of any suggestive ocular findings like uveitis (anterior, intermediate, posterior, or panuveitis), retinitis, retinal vasculitis, neuroretinitis, optic neuropathy, endophthalmitis, or panophthalmitis, living in areas of endemic TB, contact history with patients with TB diagnosis, exclusion of any other causes of uveitis, positive tuberculin skin test

(TST), evidence of healed or active lesion on chest radiography, demonstration of acid-fast bacillus (AFB) or culture of *Mycobacterium tuberculosis* from the ocular fluids, positive PCR from ocular fluids for IS 6110 or other conserved sequences of *Mycobacterium tuberculosis* genomes, positive interferon-gamma release assays (IGRAs), and a positive response to conventional antituberculous therapy (ATT) over a period of 4–6 weeks without recurrence [1, 25–28].

These guidelines categorized the ocular tuberculosis into two categories as confirmed or presumed [27–30].

In 2015, Gupta et al. proposed new guidelines which provide three categories as confirmed, probable, and possible intraocular tuberculosis [28]. This new proposed classification of intraocular tuberculosis provides more certain diagnosis with more case definition criteria [28].

Positive response to four-drug antituberculous therapy (isoniazid, rifampicin, ethambutol, pyrazinamide) in 4–6 weeks duration is defined as therapeutic test. This therapy should be started by a TB specialist and the ocular response to this therapy should be evaluated by an ophthalmologist [19, 27–30].

14.6 Ocular Imaging Techniques for Intraocular TB

Fundus fluorescein angiography is the most common imaging modality, as well as indocyanine green angiography, optical coherence tomography (OCT), orbital ultrasound, and ultrasound biomicroscopy [19, 28–29].

14.7 Medical Therapy

The current treatment of intraocular TB consists of use of four drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) taken for a long period of time (total 9–15 months) [29, 30].

Combination therapies should be preferred in order to prevent resistance. Centers for disease control (CDC) suggest four-drug therapy (isoniazid, rifampicin, ethambutol, and pyrazinamide) for 2 months, followed by two-drug therapy (isoniazid, rifampicin) for 4 months. In immunosuppressed patients two-drug therapy may be extended to 7 months [19, 31, 32].

Although ideal treatment duration is unknown, extended therapy is suggested [19, 32].

Corticosteroids may be added to four-drug ATT for 4–6 weeks to reduce the ocular damage from type IV hypersensitivity. Corticosteroids should never be used alone in order to prevent reactivation of a latent infection or flare up of the systemic infection [30].

14.8 Ocular Side Effects of Antituberculosis Drugs

Ethambutol may lead to dose-related toxicity. All patients should be evaluated for visual acuity, visual field testing, and color vision test before ethambutol therapy. Doses below 15 mg/day rarely result in ocular side effects. Most common signs for toxicity are optic neuropathy, acquired red-green dischromatopsy, central scotoma, disc edema, disc hyperemia, peripapillary splinter hemorrhages, optic atrophy, retinal edema, and pigmentary changes of the macula. Patients under ethambutol therapy should be followed up by an ophthalmologist once in every 2–4 weeks for doses over 15 mg/day and once in every 3–6 months for lower doses [19, 33].

Optic neuritis and optic atrophy are rarely reported for isoniazid [19].

Ocular TB is a masquerading disease with different clinical manifestations, with no gold standard test for a certain diagnosis. An empirical clinical approach, including evaluation of clinical symptoms, ocular and systemic examination findings, and positive laboratory results with detection of the bacillus in the intraocular fluids and tissues by direct microscopy, culture, or PCR, makes a definitive diagnosis permitting antituberculous treatment with a four-drug combination therapy in an extended duration.

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Chapter 15
Infection Control in Extrapulmonary TB

Lul Raka and Gjyle Mulliqi-Osmani

15.1 Introduction: Transmission of Tuberculosis

Tuberculosis (TB) remains one of the major global public health problems. In 2015, an estimated 10.4 million people developed TB, and 1.8 million died from the disease, 400,000 of whom were HIV-positive [1, 2].

Transmission of *M. tuberculosis* occurs from one person to another through the airborne route, when an infected person speaks, coughs or sneezes. These activities produce liquid particles called droplet nuclei, which contain *M. tuberculosis* microorganisms. Another possibility to create these droplets is during the following medical procedures: sputum induction, bronchoscopy, endotracheal intubation, drainage of tuberculous abscesses and autopsy [3, 4].

Droplet nuclei between 1 and 5 μm pose the highest risk of transmitting infection. They remain suspended in the air for longer periods of time and find their way to alveolar space. These droplets need to carry only one viable *M. tuberculosis* microorganism to transmit infection [5].

Transmission of TB is affected by the infectiousness of patient, environmental conditions and timing of exposure. The infectiousness of a TB patient depends directly from the number of droplet nuclei carrying *M. tuberculosis*. There are also some other factors contributing to the infectiousness of TB: the site of disease, the presence of productive cough and results of sputum smears, the presence of cavitation, the duration of adequate chemotherapy and willingness of the patient to cover mouth and nose during coughing.

Although airborne route is the most important route for healthcare-associated transmission of *M. tuberculosis*, occasionally there are other routes via bronchoscopes, during organ transplantation, autopsies and during injection of laboratory animals with *M. tuberculosis*.

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15.2 Infection Control Strategies

Pulmonary TB is the most common and important form of the disease from the perspective of infection control. TB infection prevention and control is structured in three levels of measures:

1. Administrative procedures, which reduce the risk of exposure to persons with infectious TB
2. Environmental controls, which reduce the concentration of infectious droplet nuclei and prevent their spread
3. Personal respiratory protection that protects HCWs during their work

The most important administrative measures include early identification of potentially infectious TB patients, prompt isolation and initiation of anti-tuberculosis treatment. Other measures include a risk assessment of transmission in the facility, preparation of infection control plan and training of HCWs to implement the plan. It is mandatory to assign one person to evaluate and monitor the implementation of the IC plan.

Exposure to infectious droplet nuclei usually cannot be totally eliminated. Therefore, various environmental control measures are used to reduce the concentration of droplet nuclei in the air. Environmental measures include ventilation, ultraviolet germicidal irradiation (UVGI) and portable air-cleaning devices.

Third component is targeting protection of HCW by reducing the risk of transmission to them or reducing the risk of disease if infection has occurred. These measures are usage of personal respirators (N95), training of HCWs on respiratory protection and training patients on respiratory hygiene and cough etiquette procedures [6, 7].

15.3 Extrapulmonary Tuberculosis

Extrapulmonary tuberculosis (EPTB) is an infection caused by *M. tuberculosis*, which affects tissues and organs outside the lungs. The AIDS pandemic has emphasised the importance of EPTB. TB can affect almost every organ in our body. The most common forms of extrapulmonary TB are lymph node TB, gastrointestinal TB, spinal TB and joint TB [8].

In majority of these extrapulmonary sites, without pulmonary or laryngeal involvement, TB is usually not contagious. However, sometimes irrigation of tuberculous lesions can produce infectious droplet nuclei resulting in transmission of *M. tuberculosis*. EPTB can be infectious when diagnostic or therapeutic procedures are performed on infected lesions.

Persons with extrapulmonary TB disease may have concurrent unsuspected pulmonary or laryngeal TB disease. Therefore, all patients with EPTB should be referred for site-specific investigation and have a chest X-ray and if possible a sputum specimen.

The clinical picture of EPTB is atypical, and therefore it is very difficult to obtain correct microbiological samples for the confirmation of diagnosis. But, nowadays the modern diagnostic methods (computerised tomographic scan, magnetic resonance, laparoscopy, etc.) provide great support in diagnosis and localization of EPTB [9].

Although evidence of transmission (other than direct inoculation) of MTB from extrapulmonary sources is lacking in the current literature, in-depth evaluations of the infectiousness and risk of transmission from extrapulmonary TB have not been adequately documented in the literature [10].

15.3.1 Tuberculous Laryngitis

Involvement of larynx is usually accompanied with pulmonary involvement and high degree of infectiosity. More than one half of cases with laryngeal tuberculosis have hematogenous origin and are infectious. Infection control activities are same as described above [6, 7].

15.3.2 Tracheobronchial Tuberculosis

Tracheobronchial tuberculosis (TBTB) is defined as tuberculous infection of the tracheobronchial tree with microbial and also histopathological evidence. Diagnosis is usually delayed due to nonspecific symptoms. Tracheobronchial stenosis is one of the most common long-term complications of TBTB. This disease is reported in approximately 10–39% of the patients with pulmonary tuberculosis. Infection control remains a challenge for these diseases. Delays in diagnosis and atypical symptoms can amplify the transmission rate of disease.

15.3.3 Tuberculosis at Autopsy

TB is an unusual finding at autopsy (about 1 case/300 autopsies), but it still poses an occupational risk being 100–200 times higher that of the general public [11].

Infection control strategies comprise:

- Appropriate autopsy room design and ventilation
- Choice of personal protective equipment
- Risk assessment of deceased
- Routine disinfection and decontamination
- Use of methods to minimise the production of infected aerosol and protection against any aerosol created
- Monitoring the health of medical staff

To prevent cutaneous TB, the Royal College of Pathologists Guidelines (http://www.rcpath.org) include recommendations on standard autopsy clothing and appropriate gloves ("doublegloving" with both latex and neoprene cut-resistant gloves), together with observation of standard precautions.

15.3.4 Spinal TB

Skeletal TB accounts for 10–20% of all EPTB, with spinal involvement in 50–60% of all skeletal TB cases. Between 50% and 75% of patients with osteoarticular TB and up to 50% of patients with spinal TB have an associated primary lung focus or have a reported history of pulmonary TB.

A total of 29 individual cases of concomitant pulmonary and spinal TB have been reported in the literature. Respiratory transmission of TB has been documented in patients with AFB smear-negative sputum. One study found that those with extrapulmonary TB increased the TB transmission rate, suggesting that the infectiousness of extrapulmonary TB has previously been underestimated [12].

The Centers for Disease Control and Prevention recommends that "persons diagnosed with extrapulmonary TB disease should be evaluated for the presence of concurrent pulmonary TB disease"; however, further description of the extent of that evaluation is lacking. According to Mandell's principles and practice of infectious diseases, a CXR should be routinely obtained in Pott's disease since abnormal radiographs can have important health ramifications [6].

Airborne isolation of patients with suspected EPTB, including spinal TB, is justified until chest X-ray and sputum smear results are known and cultures have been obtained. Although, there is documentation of AFB smear-negative transmission of pulmonary TB, it is customary to discontinue isolation once negative AFB sputum smear results are known.

Advantages of taking an aggressive approach to isolation and documentation of active pulmonary TB include minimising healthcare worker and patient exposure to a potentially infectious patient.

In conclusion, transmission and outbreaks caused by *M. tuberculosis* still represent a challenge. To address this issue, TB infection control measures should be strengthened around the world, particularly in resource-constrained countries and those with high prevalence of TB and HIV [13, 14].

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Chapter 16
Tuberculosis in the ICU

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16.1 Introduction

Tuberculosis (TB) is one of the world's most lethal diseases. In 2015, 10 million people worldwide contracted TB, and 1.8 million deaths were TB-related [1]. Although the trend in TB incidence has steadily declined in the last few years, special groups, including individuals that were homeless, prisoners, drug addicts, and foreign-born, were at the highest risk and had the least access to healthcare. In Turkey, a total of 12,772 tuberculosis cases were reported in 2015 [2].

Patients with TB are admitted to intensive care units (ICUs) at frequencies ranging from 1% to 3% [3, 4]. A timely diagnosis of TB is vital, because delayed treatment is associated with severe morbidity in the ICU. Thus, it is important for intensivists to understand the typical distribution, forms, and radiologic manifestations of TB. The incidence of TB among patients in the ICU is significantly higher than the incidence observed in the general population. Most patients with TB come to an end in the ICU, with multidrug-resistant TB. These patients have pulmonary TB and/or miliary TB with important comorbidities.

16.2 Tuberculosis Presentation in the ICU

The clinical forms of TB include TB with isolated pulmonary involvement, TB with pulmonary and extrapulmonary involvement, and TB with isolated extrapulmonary involvement. Recently, it was reported that, among patients with severe TB that required intensive care, the distribution of clinical forms was 71.8% isolated pulmonary TB, 20.5% TB involving pulmonary and

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extrapulmonary organs (genitourinary, peritoneal, meningeal, lymphatic, pleural, renal, and hematological), and 7.7% isolated extrapulmonary TB (pericardial, meningeal, and lymphatic) [4].

Severe TB that requires ICU treatment generally presents as respiratory failure, and mortality rates range from 15.5% to 65.9% [3, 5–7]. Respiratory failure associated with pulmonary TB may occur with an acute disease, such as miliary tuberculosis, acute respiratory distress syndrome (ARDS), or bronchopneumonia; or it may occur chronically, as a disease sequel. Balkema et al. [8] showed that, for two thirds of patients, the primary reason for ICU admission was acute respiratory failure, mostly due to massive hemoptysis. However, the most common radiologic finding in their study was diffuse bronchopneumonia. Most infections were pneumonia infections caused by either *Streptococcus* or *Staphylococcus aureus*. *Mycobacterium tuberculosis* is frequently associated with pulmonary bacterial infections, most often *Streptococcus pneumoniae* infections, particularly in children. The Community-Acquired Pneumonia Organization (CAPO) maintains a database on a multinational cohort of adults hospitalized with CAP. This organization reported that, of the 6976 patients with CAP, 60 (0.86%) had infections caused by *M. tuberculosis* [9]. The intensivist might see patients with *M. tuberculosis* infections that appear to have severe CAP. A failure to diagnose a patient with CAP caused by *M. tuberculosis* may have serious consequences for both the healthcare worker and the patient.

The second most frequent reason that patients with TB require ICU admission is severe sepsis/septic shock. Most of these patients present with multiple organ failure (MOF), and they exhibit a higher mortality compared to patients admitted to the ICU for other reasons. Landouzy's sepsis in disseminated TB is a rapidly progressive form of sepsis; it leads to MOF and death in an immunocompromised person, when not treated aggressively. Parisian neurologist, Louis Theophile Joseph Landouzy (1845–1917), first described this entity. This septic process typically arises in patients that are immunocompromised, but it can also occur in patients that are immunocompetent [10, 11]. However, other microorganisms must be ruled out to support the diagnosis of TB-associated septic shock or sepsis.

Some studies have reported HIV/TB coinfections in patients that are critically ill [4, 12]. Coinfections of HIV and TB occur frequently, and they are associated with greater mortality and worse outcomes than TB alone. These patients often present with atypical TB, and they may receive delayed treatment, due to diagnostic difficulties and impaired access to healthcare [4]. Severe immunosuppression, which is typically caused by HIV infections, is a known risk factor for TB [13]. Respiratory failure is the main reason for ICU admission among patients with pulmonary HIV/TB. Most of these patients present with disseminated TB. The recovery of *M. tuberculosis* from blood cultures is suggestive of disseminated TB, and 14% of patients with HIV have bacteremia. Other causes of ICU admission are severe sepsis/septic shock and coma/torpor. *M. tuberculosis* is a common etiologic agent of sepsis in populations with HIV-related disease, as observed in published studies [14, 15]. Research findings have suggested that patients with disseminated and extrapulmonary forms of TB may represent a special group that is associated with worse

outcomes. Patients that are critically ill with HIV/TB have a high 6-month mortality rate, and the risk is strongly associated with the nadir CD4 cell count. Neurological dysfunction is also associated with poor survival, even without primary central nervous system involvement [12].

16.3 Tuberculosis Diagnosis in the ICU

TB should be confirmed by culturing patient specimens, when possible. Theses culture can confirm the diagnosis and also provide a means to test drug susceptibility. Specimens that can be cultured for a TB diagnosis include sputum, bronchoalveolar lavage, tracheal and nasogastric aspirations, cerebrospinal fluid, pericardial fluid, peritoneal fluid, urine, pleural fluid, lymph node aspiration, and blood.

Chest radiography (CXR) remains the first choice for the initial evaluation of patients with TB. There are few signs specific to TB for patients in the ICU; some studies have reported that small nodules or cavitary patterns on a CXR, combined with an illness duration of more than 2 weeks, may be indicative of TB [16]. Computed tomography (CT) scanning may identify active TB. The most common CT findings are ARDS-like manifestations, parenchymal nodular infiltration and cavitation, consolidation, interstitial involvement, a calcified parenchymal mass, ground-glass opacities, and pleural effusion or thickening. Nearly 50% of adults with TB display radiologic evidence of lymphadenopathy. Among all pulmonary manifestations of TB, the highest mortality rates were associated with ARDS-like manifestations on a CT (64.5%) and miliary TB (85.5%) [17]. Most patients have non-diagnostic CXRs and only display an abnormality on CTs. When considered early, CT scanning could substantially increase the ability to diagnose active TB. Many patients with active TB have been misdiagnosed and were given the wrong treatment.

16.4 Treatment for Patients with Tuberculosis in the ICU

Patients with infections should be isolated in rooms with negative pressure, and visitors should be limited. The isolation time will depend on the period of replication of the microorganism, the patient's status, and the patient's comorbidities, such as immunosuppression. A definite TB diagnosis is not always simple. When there is a suspicion of TB, treatment should be started immediately without waiting for culture results. Moreover, treatment should be continued, even when the first culture results are negative, and the clinician should continue to collect appropriate samples for culturing.

Acute TB is conventionally treated immediately with anti-tuberculosis chemotherapy and, when required, mechanical ventilation. Good results have also been achieved with noninvasive pressure support ventilation (NIPSV) and other adjuvant

therapies [18, 19]. Adjunctive corticotherapy, like that used in meningeal or pericardial disease, was associated with survival in patients with TB [20]. Steroids might be effective in reducing mortality for all forms of TB that require intensive care admission, including pulmonary TB. Corticosteroids can reduce the 90-day mortality in patients with pulmonary TB, when admitted to the ICU due to acute respiratory failure [21].

In the event of either acute or chronic respiratory failure secondary to pulmonary TB, a patient might require ventilator support. Extracorporeal membrane oxygenation (ECMO) has been useful in several scenarios for maintaining oxygenation and perfusion in patients with irreversible cardiorespiratory failure. For patients with TB, ECMO was shown to be useful in cases of refractory shock, renal failure, liver dysfunction, and ARDS [11]. Alternatively, in selected patients, the need for invasive ventilation may potentially be avoided with careful use of noninvasive ventilation (NIV) in acute situations. However, the use of NIV in acute situations is associated with a potential risk of TB spreading [18, 22]. The intensivist must carefully weigh the potential benefits and risks, before deciding whether to initiate NIV or invasive ventilation in acute respiratory failure due to pulmonary TB. The risks related to positive pressure ventilation, such as hemoptysis and pneumothorax, should be taken into account [22].

16.5 Tuberculosis Outcome and Mortality in the ICU

Active TB that requires ICU treatment generally presents as respiratory failure that requires mechanical ventilation. Despite the availability of effective therapies, mortality rates for patients with TB in the ICU remain between 15.5% and 65.9% [3, 5–7]. This rate is more than twice that observed in patients with respiratory failure due to CAP [9].

Several studies have shown an association between delays in commencing antituberculosis treatment and mortality [8]. It was reported that a 3–4-day treatment delay in hospital was related to a mortality rate of 33% for patients with TB in acute respiratory failure. The interval between ICU admission and anti-tuberculosis drug initiation was shorter in the group of survivors than in the group of nonsurvivors [23].

ICU mortality has been significantly associated with age, mechanical ventilation, MOF, ARDS, sepsis, vasoactive drugs, renal replacement therapy, a low Glasgow score, a high Simplified Acute Physiology Score (SAPS) II, a high Sequential Organ Failure Assessment (SOFA) Score, lymphopenia, hypoproteinemia, low serum albumin levels, and two concomitant non-tuberculous infections [3, 6–9]. Failure of any organ can negatively affect the TB prognosis, and it is associated with increased mortality. However, among all potential organ dysfunctions, neurological dysfunction occurred more frequently in non-survivors than in survivors, even after excluding patients with primary CNS involvement [6]. HIV positivity was not a risk factor for mortality; a recent study reported a trend of improved ICU survival among

patients with HIV/TB coinfections [6]. Among patients with HIV/TB coinfections, only a CD4 count of <200 cells/mm^3 and the absence of lobar consolidation were associated with ICU mortality [8].

Some studies evaluated outcome in patients with TB, stratified by the type of radiologic pulmonary manifestations. They found that, among all pulmonary manifestations, miliary TB (85.5%) and ARDS (64.5%) had the highest mortality rates [17].

In conclusion, most factors associated with the risk of mortality in patients with TB are connected to the severity of organ failure. Other mortality risk factors (such as nosocomial infections) were actually related to intensive care processes. Clinical measures for managing TB should be aimed at supporting early diagnosis and treatment. An early TB diagnosis can contribute to better outcomes and, at the same time, break the chain of transmission.

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