Extrapulmonary Tuberculosis

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Pathogenic Mycobacterium tuberculosis complex organisms (MTBC) primarily cause pulmonary tuberculosis (PTB); however, MTBC are also capable of causing disease in extrapulmonary (EP) organs, which pose a significant threat to human health worldwide. Extrapulmonary tuberculosis (EPTB) accounts for about 20–30% of all active TB cases and affects mainly children and adults with compromised immune systems. EPTB can occur through hematogenous, lymphatic, or localized bacillary dissemination from a primary source, such as PTB, and affects the brain, eye, mouth, tongue, lymph nodes of neck, spine, bones, muscles, skin, pleura, pericardium, gastrointestinal, peritoneum, and the genitourinary system as primary and/or disseminated disease. EPTB diagnosis involves clinical, radiological, microbiological, histopathological, biochemical/immunological, and molecular methods. However, only culture and molecular techniques are considered confirmatory to differentiate MTBC from any non-tuberculous mycobacteria (NTM) species. While EPTB due to MTBC responds to first-line anti-TB drugs (ATD), drug susceptibility profiling is an essential criterion for addressing drug-resistant EPTB cases (DR-EPTB). Besides antibiotics, adjuvant therapy with corticosteroids has also been used to treat specific EPTB cases. Occasionally, surgical intervention is recommended, mainly when organ damage is debilitating to the patient.

Keywords: lymph node ; meningitis ; lymphadenitis ; pericarditis ; cutaneous ; genitourinary ; miliary

1. Introduction

Tuberculosis (TB) is a significant cause of morbidity and mortality among humans worldwide. *Mycobacterium tuberculosis* complex organisms (MTBC) cause TB primarily in the lungs (pulmonary TB; PTB) but can also affect other organs, causing extrapulmonary tuberculosis (EPTB). Common disease manifestations of EPTB include meningitis, lymphadenitis, ocular, oral, pleuritis, pericarditis, peritonitis, cutaneous, musculoskeletal, abdominal, genitourinary, and miliary forms of tuberculosis (Table 1). EPTB cases accounted for 16% of the 7.5 million incident cases worldwide in 2019 [1]. EPTB can be either primary (at the site of initial infection) or secondary (disseminated), which usually occurs due to hematogenous or lymphatic spread of bacteria from the primary organ, reactivation of latent TB (LTBI), ingestion of infected sputum, or spread locally from adjacent organs [2][3]. The diagnosis and treatment of EPTB are challenging. Most cases show constitutive symptoms such as fever, weight loss, night sweats, or malaise with specific systemic symptoms based on the organ affected. In general, symptomatic patients are subjected to radiologic imaging of the infected organs to evaluate and plan a more accurate and specific diagnostic test. Usually, the extrapulmonary sample obtained by fine-needle aspiration or biopsy is used for microscopy, histopathology, culture, biochemical/immunological, and molecular testing, including drug susceptibility, to start an effective treatment [2][3][4]. The sensitivity and specificity of various tests used to diagnose EPTB are highly variable; in most cases, clinical disease presentation should be considered in choosing and interpreting a specific diagnostic test. The treatment regimen for EPTB is the same as that for PTB for drug-sensitive and resistant cases; however, brain or bone involvement prompts a more extended treatment than PTB. Considering the clinical significance of EPTB, it is vital to provide a comprehensive and cohesive review of various diagnostic modalities, treatment options, and complications associated with managing these poorly understood diseases. In this review, we summarize the recent developments in the diagnosis and treatment of EPTB.

Table 1. Summary of EPTB disease, organs affected, clinical presentation, age of onset, and recommendations for adjuvant therapy or surgery.

Disease	Organ Affected	Clinical Presentation	Age of Onset	Recommendations for Adjuvant Therapy	Recommendations for Surgery
Meningitis	Brain	Initial—headache, low-grade fever, malaise, vomiting, and confusion Severe—seizures, coma, and stupor	Children ≤5 years of age	Prednisone or dexamethasone-intravenous and continued as an oral treatment	None
Cervical Lymphadenitis	Neck-Lymph nodes	Unilateral single or multiple painless lumps; fever, night sweats, and weight loss	Adults of age 20 to 40 years	None	Incision and drainage
Ocular	Eye	Primary—eyelid, conjunctival, corneal, and scleral lesions Secondary—inflammation of the uveal tract, retina, and optic nerve	None in particular	Oral prednisone or topical steroids or prednisone drops	None
Oral	Mouth, tongue	Primary—painless ulcer, single and associated with lymph node enlargement Secondary—single, irregular, superficial, or deep painful ulcer, odynophagia	Primary—children and young adults Secondary—adults	Topical anti-inflammatory drugs or mucosa protecting agents	None
Pleural	Pleura covering the lungs	Fever, chest pain, cough, dyspnoea sometimes associated with weight loss, loss of appetite, and malaise	Adolescents and adults	None	Thoracentesis
Pericarditis	Pericardium covering the heart	Pericarditis presents as fever, weight loss, night sweats, cough, chest pain, and breathlessness, along with moderate to high pericardial effusion	Adults	Use of corticosteroids	Echocardiographic or fluoroscopic-guided needle pericardiocentesis

Disease	Organ Affected	Clinical Presentation	Age of Onset	Recommendations for Adjuvant Therapy	Recommendations for Surgery
Cutaneous	Skin	Usually presents as a reddish or purple papule or nodule accompanied by painful ulcers on the skin; occasional draining sinus tracts or cutaneous abscesses seen No fever, weight loss, or night sweats	TB cutis miliaris disseminate occurs in infants and children with less immunity;	None	Surgical excision and debridement
Musculoskeletal	Muscle and Bone *	Pain and swelling of the spine, hip, knee, shoulder, ankle, elbow, femur, humerus, hand, feet, or wrist; occasional fever, weight loss, and night sweats	Primary—children Secondary—elders	None	Surgery when neurological deficit, cord compression, spinal instability, or kyphosis to variable extent particular children; for cold abscesses and sinus tract involvement, debridement and/or drainage is conducted
Abdominal	GI tract, Peritoneum, Solid viscera	Symptoms are abdominal pain, fever, anorexia, nausea, vomiting, and diarrhoea Specific organs show perforations, obliterations, ulceration, hypertrophy, ulcerohypertrophy, fistulae, and strictures	Adults	None	Surgery when irreversible constrictions, strictures, abscesses, and fistula formation cause organ damage

Disease	Organ Affected	Clinical Presentation	Age of Onset	Recommendations for Adjuvant Therapy	Recommendations for Surgery
Genitourinary	Kidneys, male or female genital tract	Urinary tract involvement with fever, weight loss, and sweating are observed along with urologic symptoms such as flank pain, pyuria, hematuria, and even urinary incontinence Male genital tract infection shows tender scrotal swelling, irregular/nodular prostate, genital ulcer, and perineal sinus or fistula and may lead to male infertility; female genital tract shows menstrual irregularity, abdominal pain, pelvic inflammatory disease and even infertility	Adults	None	Ablative surgery; reconstructive surgery; percutaneous drainage
Miliary	Different parts of the body	The symptoms are fever, malaise, anorexia, weight loss, cough with chills, and rigours when septicaemia is involved Specific symptoms are observed depending on the organ involved and usually show cutaneous lesions (Tuberculosis cutis miliaris disseminate), choroidal tubercles, and commonly TB meningitis; atypical manifestations are also seen	Infants and children as well as elders with comorbidities; predominantly males	Prednisone when meningitis, pleuritis, or pericarditis is involved	Surgery when organ damage is irreversible

Note: All EPTB conditions listed in the table can occur as primary (rare) or secondary (common) infections, with some showing differential clinical presentation.

2. Extrapulmonary Tuberculosis of the Head and Neck

The EPTB of the head and neck comprise meningitis (brain), cervical lymphadenitis (neck), ocular (eye), and oral (mouth and tongue).

2.1. Tuberculous Meningitis

The central nervous system (CNS) involvement is the most severe form, accounting for 5–10% of all EPTB cases, with TB meningitis (TBM) being the predominant condition. TBM is common in children (below four years of age) and immunosuppressed individuals such as those with human immunodeficiency virus (HIV) infection and can occur with or without an associated PTB. Besides TBM, intracranial tuberculoma, tuberculous brain abscesses, arachnoiditis, increased intracranial pressure, and hydrocephalus were noted in CNS disease [5][6]. The onset of TBM manifests in neurological complications, such as headache, low-grade fever, malaise, vomiting, and confusion. When untreated, TBM can cause seizures, coma, and stupor. These clinical signs correspond to stage I (fully conscious and no focal deficits); stage II (conscious but with lethargy, confusion, and mild focal neurological symptoms, such as cranial nerve palsy or hemiparesis); and stage III (stupor, seizures, coma, palsies, or hemiplegia). Prognosis is dependent on the stage of diagnosis and treatment [5][6][7]. Diagnosis of TBM usually depends on clinical symptoms, radiologic imaging such as computerized tomography (CT) scan, and the presence of extra-neural TB. Usually, the cerebrospinal fluid (CSF) of patients is analyzed for disease markers. In general, predominant lymphocyte presence (60–400 cells/mL), elevated protein levels (0.8–4 g/L), a decrease in sugar levels (18–45 mg/dL), and an adenosine deaminase (ADA) level of 5–15 IU/L are indicators of suspected TBM [8][9]. Furthermore, a recent retrospective study indicated that a higher CSF protein level was associated with poor TBM prognosis in children [10]. The sensitivity and specificity of ADA are 86–89% and 78–91%, respectively, in diagnosing TBM using CSF [11][12]. Measurement of interferon-gamma (IFN-γ) levels had a sensitivity and specificity of 83% and 85%, respectively, and the same features reported 76% and 88%, respectively, for T-SPOT-TB using CSF samples [13][14]. Due to the paucibacillary nature of MTBC at the disease site in TBM, microbiological diagnosis is very challenging. The bacteriological confirmation rate of TBM diagnosis ranges between 10% and 87% of cases [8][15]. However, the acid-fast bacilli (AFB) test's sensitivity is <25%, and culture is 25–70% with 100% specificity in the CSF of TBM cases [9].

Magnetic resonance imaging (MRI) is considered superior to CT for the neuroradiology diagnosis of TBM [16][17]. The sensitivity and specificity of polymerase chain reaction (PCR)-based TBM diagnostic tests are 48–100% and 38–100%, respectively [9]. Multiplex PCR assays using MPT64 and IS6110 primers of *Mycobacterium tuberculosis* (Mtb) have shown 71.4% sensitivity and 89.6% specificity in the rapid diagnosis of TBM [18]. The loop-mediated isothermal amplification (LAMP) assay targeting IS6110 and MPB64 reported a sensitivity of 76% and specificity of 99% for CSF samples [19]. Molecular diagnostic tools, such as Xpert MTB/RIF and Xpert Ultra, are reported to have a 70% and 87% sensitivity, while 97% and 88% specificity, respectively, for adult CSF samples over smear microscopy/culture referred to as microbiological reference standard (MRS). In children, Xpert MTB/RIF has 54% sensitivity and 94% specificity over MRS. The World Health Organization (WHO) recommends Xpert MTB/RIF over smear microscopy/culture as the initial test for detecting TBM using CSF in adults and children [20]. Though line probe assays (LiPA) have been used for TBM diagnosis, more studies are needed to establish this test's sensitivity to use directly on CSF samples [21][22]. Although a single, positive diagnostic test is helpful, confirmatory diagnosis of CNS-TB cases most often requires a spectrum of tests (Table 2).

Table 2. Sensitivity and specificity of various diagnostic tests commonly used for EPTB.

Type of EP-TB	Sample	Diagnostic Test	Sensitivity	Specificity	References
Meningitis	CSF	CSF ADA	86–89%	78–91%	[11][12]
		IFN-γ	83	85	[13]
		T-SPOT-TB	76	88	[14]
		Smear	<25%	NA	[9]
		PCR-based	48–100%	38–100%	[9]
		Multiplex PCR	71.4	89.6	[18]
		LAMP	76	99	[19]
		Xpert MTB/RIF	70	97	[20]
		Xpert Ultra	87	88	[20]
Lymphadenitis	Lymph node aspirate	ADA	NA	NA	
		FNAC	88–96	88–96	[23]
		T-SPOT-TB	91	74	[24]
		Smear	34.6–66.0%	87.50%	[25]
		PCR-based	42	89.2	[26]
		LAMP	80	NA	[19]
		Xpert MTB/RIF	89	86	[20]
		Xpert Ultra	70	100	[20]
Pleural TB	Pleural fluid	Pleural ADA	88.37	88	[27]
		Pleural IFN-γ	86.61	90.2	[28]
		T-SPOT-TB	92.86	92.16	[28]
		PCR	82	85	[29]
		Multiplex PCR	95.34		[30]
		LAMP	25–75.8	83.3–100	[19]
		Xpert MTB/RIF	50	99	[20]
		Xpert Ultra	71	71	[20]
TB Pericarditis	Pericardial fluid	Pericardial ADA	87–93	89–97	[31]
		Pericardial IFN-γ	87–95	91–97	[32]
		PCR	15	100	[33]
		T-SPOT-TB	92.3	87.9	[34]
		Xpert MTB/RIF	60	88	[20]
		Xpert Ultra	NA	NA	
Cutaneous	Skin biopsy	TST	33–96%	62.50%	[35]
		Culture	74.3	NA	[36]
		PCR-based	25	73.7	[37]
		Xpert MTB/RIF	NA	NA	
		Xpert Ultra	NA	NA	

Type of EP-TB	Sample	Diagnostic Test	Sensitivity	Specificity	References
Musculoskeletal	Synovial fluid	Synovial ADA	83.3	96.7	[38]
		T-SPOT-TB	83	86	[39]
		PCR	82.65	91	[40]
		LAMP	85.3	NA	[19]
		Xpert MTB/RIF	97	94	[20]
		Xpert Ultra	96	97	[20]
Abdominal	Peritoneal fluid	ADA	100	97	[31]
		T-cell IFNγ	90	78	[41]
		PCR	35–65	100	[42]
		Multiplex PCR	75.7	100	[42]
		Xpert MTB/RIF	59	97	[20]
		Xpert Ultra	NA	NA	

Abbreviations: CSF, cerebrospinal fluid; PCR, polymerase chain re-action; LAMP, loop-mediated isothermal amplification; ADA, adenosine deaminase; IFN-γ, interferon-gamma; FNAC, fine-needle aspiration cytology; NA, not available; MTB, *Mycobacterium tuberculosis*; RIF, rifampin; TST, tuberculin skin test.

2.2. Tuberculous Lymphadenitis

Tuberculous lymphadenitis (TBL), commonly called Scrofula, is the most common form of EPTB, constituting 35–40% of EPTB [43][44]. The disease is mostly non-fatal and presents as unilateral single or multiple painless lumps, usually affecting the cervical lymph node in 60–90% of TBL cases. The submandibular and supraclavicular lymph nodes are involved in a few instances [43][44]. TBL usually more frequently occurs in individuals with a previous TB history than individuals without a prior TB history and affects the age group of 20 to 40 years. Typical TB symptoms, such as fever, night sweats, and weight loss, were observed in some patients [45][46].

The specimens' paucibacillary nature makes TBL diagnosis challenging and necessitates a combination of clinical, radiologic, microbiological, and molecular diagnostic tests to confirm the disease [47][48]. A combination of cytology (positive for epithelioid cell granulomas, multinucleated giant cells, a granulomatous lesion with caseation and necrosis), and AFB identification in the specimen can also help to diagnose TBL. The fine-needle aspiration culture (FNAC) has a specificity of 88–96%, while the smear has 34.6–66.0% sensitivity and 87.5% specificity in diagnosing TBL [23][25]. Imaging techniques such as CT or MRI can be used as an adjunct diagnostic tool for TBL [49]. However, imaging alone is insufficient to discriminate TBL from other necrotic lymphadenopathies. Therefore, patients' clinical presentation and demographics should be considered for interpreting the imaging results of TBL cases [50]. PCR diagnosis using IS6081 showed 42% sensitivity and 89.2% specificity, while LAMP using IS6110 and MBP64 had 80% sensitivity [19][26]. T-SPOT-TB has 91% sensitivity and 74% specificity for TBL diagnosis [24]. Xpert MTB/Rif and Xpert Ultra have 89% and 70% sensitivity and 86% and 100% specificity, respectively, over MRS for lymph node aspirates. These tests' sensitivity and specificity were 78% and 90–100%, and 78% and 38–87%, respectively, over MRS for adult lymph node biopsy sample (Table 2) [20].

2.3. Ocular Tuberculosis

Ocular tuberculosis (OTB) broadly refers to Mtb infection of the eye, in and around its surface. The disease can be primarily in the eyes or secondary spreading through blood supply from elsewhere. Primary progressive TB of the eye is rare, and most of the OTB cases involve exogenous infections of the eyelids, conjunctival, corneal, and scleral lesions, while the secondary disease is more common and affects the uveal tract, retina, and optic nerve. Uveitis is the most common EPTB due to the vascular supply and presents as anterior, intermediate, posterior uveitis, and pan-uveitis [51][52][53].

As patients do not usually present with other symptoms of classical TB, diagnosis is very challenging. Ophthalmic examination and a blood test for white blood cell (WBC) counts and inflammation markers are the first indicators of OTB diagnosis. Since ocular TB is very unusual, no molecular diagnostic test has been explicitly indicated for OTB diagnosis. Therefore, imaging techniques—including fluorescein and indocyanine angiography, fundus autofluorescence imaging,

optical coherence tomography, fundus fluorescein angiography, ultrasonography, and microperimetry— are extensively used to assess the extent of damage to the eye as well as a therapeutic response [54][55]. The patient's prior TB history is reviewed to rule out other reasons before tests specific to OTB are performed for uveitis. Retrieving samples from the eye is challenging, and in most instances, they are paucibacillary. Microbiological testing involving smear, culture, and molecular diagnosis is performed from the aqueous and vitreous samples obtained from the eye. A smear or culture from the specimen's biopsy from eyelids, conjunctiva, and lacrimal glands can prove confirmatory. If direct smear test of the sample fails to show any bacteria, then a culture is grown from the sample to confirm bacterial presence. Histological analysis of samples from fluids or tissue reveals granulomas and caseating necrosis irrespective of the presence of AFB [51][56][57]. Molecular diagnosis involves using multiplex PCR and real-time PCR for Mtb MBP64, and IS6110 and protein b using aqueous samples, vitreous samples, subretinal fluid, and tissue specimens showed a sensitivity and specificity of 77.77% and 100%, respectively. qPCR for MBP64 was reported in few case reports of uveitis [58]. LAMP assay targeting *mbp64* gene using aqueous and vitreous samples showed sensitivity and specificity of 85.7% and 100%, respectively [59]. MTBDRplus was tested for intraocular tuberculosis with 36% sensitivity and 100% specificity [60]. Xpert MTB/RIF showed a sensitivity of 23% and specificity of 100% for intraocular tuberculosis [61].

2.4. Oral Tuberculosis

Oral tuberculosis (OrTB) is another rare form of EPTB and can occur as a primary or secondary infection. Primary infections are uncommon and usually seen in children and young adults with painless ulcers, single and associated with lymph node enlargement more commonly in the gingiva than the tongue. It is related to a trauma of the affected area (inflammation or irritation) [62][63][64][65]. The secondary infection is more common and usually associated with a PTB. They are seen as single, irregular, superficial, or deep painful ulcers, odynophagia, and sometimes associated with mandible or maxillary bone TB. The infection can occur due to inoculation of the oral cavity by Mtb from sputum or hematogenous spread from other primary sites [64][66][67][68][69]. The tongue is most commonly affected in OrTB, while any oral mucosa including palate, lips, buccal mucosa, gingiva, palatine tonsil, and mouth floor could be involved. Constitutional symptoms are rare in OrTB [70][71][72]. Tonsillar TB is extremely rare and hence clinically missed out. It presents with chronic tonsillitis and sore throat and is a secondary form of EPTB [73]. Pharyngeal TB is another sporadic form of EPTB, which presents as a neck mass, nasal blockage, fever, and night sweats and is usually a secondary form of EPTB [74].

The differential diagnosis of oral tuberculosis is complicated by ulcers that are more common in primary syphilis, severe fungal disease, and non-infectious conditions, such as traumatic ulcers or squamous cell carcinoma. The biopsy of the specimen becomes the best criteria for assessing OrTB. X-rays of the mandible and maxilla are performed where TB osteomyelitis is suspected. The AFB and culture of the biopsy sample are confirmatory for the presence of Mtb, although smears could be negative in many cases [65][66][67][68][75]. Histopathology of biopsy indicates caseating granuloma with central necrosis, surrounded by epithelioid cells, Langhans type of giant cells, and lymphocytes infiltration, while in immunocompromised cases, a non-caseating granuloma is seen [70][71][72]. Fine-needle aspiration cytology has also been used to confirm OrTB [55][76][77]. Molecular methods involving PCR have also been explored to diagnose OrTB, but no data are available on its sensitivity or specificity [63][78]. However, the application of Xpert MTB/RIF, LAMP, or LiPA for OrTB diagnosis has not been reported.

3. Extrapulmonary TB of the Thorax

EPTB of the thorax includes pleuritis (pleura) and pericarditis (pericardium).

3.1. Pleural Tuberculosis

Pleural tuberculosis (PLTB) is one of the common forms of EPTB associated with PTB as an immune reaction or miliary TB. PLTB is rare in children 2–12 years old and is commonly found in adolescents 12–16 years old and adults [79][80][81]. The typical clinical features are fever (in about 86% of cases), chest pain, cough, and dyspnoea, and it is sometimes associated with loss of appetite, malaise, and weight loss, [82].

Diagnosis involves a combination of clinical, radiological, microbiological, and molecular testing. Non-invasive tests such as chest X-ray, ultrasonography, CT, MRI or fluorodeoxyglucose-positron emission tomography (FDG-PET) reveal pleural effusion, the extent of pleural wall thickening, differential diagnosis of parenchymal lesions, and mediastinal lymph nodes. CT, MRI, and FDG-PET help rule out other clinical conditions, such as pneumonia, inflammation, or malignancy associated with pleural effusion and thickening. Further, thoracentesis is required for the therapeutic drain of pleural fluid, especially in large effusions, and a cutting needle pleural biopsy is performed when thoracentesis is inconclusive. This pleural fluid or biopsy sample can be used to diagnose PLTB further. Besides the pleural sample, a sputum sample is induced and collected for further diagnosis [79][83][84]. Two biochemical parameters, ADA and interferon-γ (IFN-γ) levels,

are monitored in pleural fluid, and elevated levels of these markers help PLTB diagnosis in high prevalence or endemic settings. In endemic countries, pleural ADA levels of >40 IU/L have a positive predictive value of 98% [85]. With a cut-off value of 40.68 IU/L, the assay had 88.37% sensitivity and 88% specificity [27][86]. A recent study reported that the ratio of lactate dehydrogenase to ADA ratio (LDH/ADA) of ≤10 has a specificity of 90% and sensitivity of 78% for PLTB diagnosis in high TB incidence settings [87]. While interferon-γ levels at a 95 ng/ml threshold are reported to give 86.61% sensitivity and 90.2% specificity in diagnosing PLTB, T-SPOT-TB has a sensitivity of 92.86% and specificity of 92.16% for PLTB (Table 2) [28]. The presence of AFB in smears and culture of mycobacteria from pleural fluid or induced sputum is confirmatory of PLTB. Moreover, establishment of epithelioid granuloma or caseating granuloma in a pleural biopsy indicates PLTB [82][84][88]. PCR (IS6110) has a sensitivity of 82% and sensitivity with multiplex PCR (MBP64 and IS6110) showing improved sensitivity of 95.34% [29][30]. LAMP assays targeting IS6110 and MPB64 reported 25–75.8% sensitivity and 83.3–100% specificity [19], while the MTBDRplus showed 44% sensitivity and 98.9% specificity when tested directly on samples [89]. Xpert MTB/RIF can be used as an initial test for adults and children with EP-TB indications using a pleural fluid sample. The Xpert MTB/RIF and Xpert Ultra sensitivities are 50% and 71% over MRS with 99% and 71% specificity, respectively, for adult pleural fluid (Table 2) [20].

3.2. Tuberculous Pericarditis

Tuberculous pericarditis (TBP) is an uncommon manifestation of TB and a cause of mortality without proper diagnosis and treatment. TBP usually develops through the hematogenous spread and retrograde lymphatic spread of Mtb from peritracheal, peribronchial, or mediastinal lymph nodes or primary or secondary TB. TBP has three clinical forms: pericardial effusion, constrictive pericarditis, and a combination of effusion and constriction. Pericardial effusion is marked by fever, weight loss, night sweats, cough, chest pain, and breathlessness, along with moderate to high pericardial effusion. In the next stage, constrictive pericarditis is seen along with thick fibrinous fluid around the heart. Constrictive pericarditis is seen as a constriction of the heart secondary to pericardial inflammation and edema [90][91][92]. HIV co-morbidity has shown a rise in TBP due to increased hematogenous spread [91][93][94].

The diagnosis of TBP is very challenging. Chest X-ray, electrocardiogram, and echocardiogram are essential for diagnosing pericarditis. The definitive diagnosis involves the presence of AFB on smear or culture of pericardial fluid or caseating granulomatous lesions in the histopathology of pericardium samples [90]. However, due to the paucibacillary nature of pericardial effusion and the hazardous invasive pericardial biopsy procedure, other options need to be considered. ADA and IFN-γ measurement above 40 U/L and 50 pg/mL in the pericardial fluid is reported useful in diagnosis [95]. Diagnosis using pericardial ADA levels had 87–93% sensitivity and 89–97% specificity [31], while the sensitivity and specificity for IFN-γ were 87–85% and 91–97%, respectively, and the T-SPOT-TB showed 92.3% sensitivity and 87.9% specificity for TBP diagnosis (Table 2) [32][34]. Multiple imaging methods such as CT, MRI, cardiac magnetic resonance, and FDG-PET have been used for TBP diagnosis [96][97][98][99]. A previous report using IS6110-PCR had a sensitivity of 15% and specificity of 100% [33]. Since Xpert MTB/RIF has a sensitivity of 60% and specificity of 88% over MRS in adult pericardial fluid samples, it can be used as an initial diagnostic test (Table 2) [20].

4. Extrapulmonary TB of Skin, Bone and Muscle

Common EPTB that affects skin, soft tissues, and musculoskeletal structures (bones and muscles) are discussed here.

4.1. Cutaneous Tuberculosis

Cutaneous or skin tuberculosis (CTB) constitutes 1–1.5% of all EPTB. The primary source of CTB could be exogenous, endogenous, or through hematogenous spread. In an exogenous spread, there is a direct TB inoculation or tuberculous chancre. The bacilli enter through minor skin abrasions or broken skin onto a person previously uninfected by Mtb. Over 2 to 4 weeks post-inoculation, the infection develops as a non-tender nodule that enlarges and erodes into a painless ulcer. When the same happens in a person with pre-existing immunity to TB, it occurs as TB verrucosa cutis, which manifests as a painful hyperkeratotic or verrucous papule with an inflammatory areola. CTB due to endogenous source (known as scrofuloderma) occurs on the skin as a contiguous extension of underlying TB, usually lymphadenitis or bone or joint or epididymis TB. This lesion appears as a subcutaneous swelling or nodule that gets attached to overlying skin and eventually develops draining sinus tracts that drain watery, purulent, or caseous material or cutaneous abscesses [100][101][102][103]. Orificial TB is a less common manifestation of cutaneous TB. The infection spreads from advanced pulmonary, intestinal, or genitourinary TB and causes painful ulcerative disease near orifices such as oral, perineal, and perirectal skin [100][101][102][103]. Lupus vulgaris is the chronic form of CTB that produces lesions of individual plaques or nodules with some ulceration and scarring [100][101][102][103]. Recent studies have reported atypical clinical presentations, such as diffused facial granulomas and scrofuloderma of cheek and neck among CTB cases [104][105]. A less common form of hematogenous spread from a pulmonary source in infants and children results in TB cutis miliaris disseminate. It occurs in

immunocompromised individuals, such as those with HIV or an exanthematous disease, such as measles or scarlet fever. Lesions are usually blue to brownish papules capped by vesicles and spread over the trunk, thighs, buttocks, and genitalia [100][101][102][103]. Tuberculous mastitis is a rare condition seen as solid, non-tender nodule or mass in the breast due to lymphatic involvement of underlying lymph nodes [100][101][102][103].

Diagnosing CTB is very challenging and involves history, clinical presentation, laboratory diagnosis, smear, culture, histopathology, and molecular diagnosis from the lesions. TSTs have shown 33–96% sensitivity and 62.5% specificity for CTB [35]. Skin biopsy is an ideal sample for CTB diagnosis by AFB staining and/or the bacilli culture. A study using Lowenstein–Jensen (LJ) and BACTEC systems to diagnose CTB cases including lupus vulgaris, scrofuloderma, tuberculosis verrucosa cutis, and scrofulous gumma showed a pooled sensitivity of 74.3%, indicating that culture is essential for CTB diagnosis [106]. The molecular test involving PCR is a rapid and easy diagnosis of cutaneous TB. The sensitivity and specificity of a PCR test using MBP64 to diagnose skin biopsy is 25% and 73.7%, respectively (Table 2) [37]. Histopathology reveals lymphocytes, epithelioid histiocytes, and Langerhans giant cells. However, different forms of CTB differ in their granuloma presentation. Tuberculous chancre, tuberculosis verrucosa cutis, and orificial TB show granulomas with caseous necrosis of moderate intensity, while necrotizing neutrophilic infiltrate is seen in tuberculosis chancre. Lupus vulgaris shows well-formed granulomas with rare necrotic caseation, while scrofuloderma has less intense granuloma with predominant caseating necrosis [35][100][102][107].

4.2. Musculoskeletal Tuberculosis

Musculoskeletal TB (MSTB) is a common form of EPTB with the involvement of skeletal, muscular, and musculoskeletal components. In general, MSTB remains guile for long periods, and there is a delay in the differential diagnosis as TB. The musculoskeletal involvement is mostly due to the hematogenous spread of primary disease in children, typically in TB endemic countries, and reactivation of LTBI in adults in developed countries [108]. Osteoarticular lesions usually occur in MSTB due to hematogenous spread from the primary site of infection. Any bone, joint, or bursa can be infected, but the major weight-bearing bones, such as the spine, hip, and knee, are the most prevalent infection sites, representing 70% to 80% of MSTB cases [109]. Vertebral or spinal TB is the most predominant form of MSTB, with an incidence of 1–2% of all TB cases [109][110]. Spinal TB (also called Pott's disease) clinically manifests into constitutional, localized, or both. Constitutional symptoms usually mimic active TB and occur in 20–30% of MSTB cases and include fever, malaise, loss of body weight, and night sweats [108][111][112][113]. In about 90% of spinal TB cases, back pain was the most common symptom. Spinal deformity and associated paraplegia and kyphosis of varying degrees have been observed in children and adults with MSTB [108][114][115]. Paraspinal abscesses are quite common in vertebral TB, occurring in more than 90% of cases. The abscess may extend to adjacent ligaments and soft tissues as well as the epidural space [108][112][113]. Neurologic deficits are usually associated with children, while adults with spinal TB have a weakness, numbness, tingling sensation, and loss of motor functions [114][116].

Apart from the spine, other major bones are involved and result in a range of conditions, such as tuberculous arthritis, tuberculous osteomyelitis, tuberculous tenosynovitis, and prosthetic joint infections. Tuberculous arthritis usually affects major joints, including the hip and knee, along with other joints such as the shoulder, ankle, elbow, and wrist, but in all cases, it is mostly monoarticular. The clinical symptoms include slow progressive painful swelling, synovial hypertrophy, and effusion [108][117]. Tuberculous osteomyelitis usually occurs in conjunction with tuberculous arthritis, although it can be independent of joint involvement. In adults, long bones such as femur or humerus are typically affected, while in children, it is usually short bones of the hands and feet, resulting in tuberculous dactylitis [118][119][120][121][122]. Tenosynovitis usually occurs in association with skeletal TB and involves the tendon sheath of hands and wrist. Carpel tunnel syndrome is a common form of tuberculous synovitis [123][124]. Previous studies have shown the involvement of various bones—including vertebral (49–54%), joints (26%), knee (13–18%), hip (8–16%), ankle/foot (8%), elbow (4%), and wrist involvement (1–4%)—and joints to various proportions [125][126].

Differential diagnosis of MSTB is conducted by clinical and radiologic examination. Imaging of the affected area is performed using conventional X-rays, CT, or MRI to assess the damage. Fine-needle aspiration or biopsy of the affected site is recommended for microbiological and histological diagnosis of MSTB. Using the sample, AFB, culture, as well as molecular testing and histopathology are carried out. In addition, the synovial fluid ADA levels can be helpful in TB diagnosis with a cut-off value of ≥31 U/L. The sensitivity and specificity for the ADA test have been indicated at 83.3% and 96.7%, respectively, for TB arthritis [38]. A pilot study of IGRA using T-SPOT-TB for TB arthritis has shown a specificity of 83% and specificity of 86% when used for the synovial fluid mononuclear cells [39]. A previous study on joint TB has reported a sensitivity of 82.65% and specificity of 91% using PCR [40]. Since Xpert MTB/RIF and Xpert Ultra have a sensitivity of 97% and 96% with a specificity of 94% and 97%, respectively, over MRS in the adult synovial fluid sample, they may be used as an initial diagnostic test (Table 2) [20].

5. Tuberculosis of the Abdomen and Genitourinary System

This section includes the abdominal (gastrointestinal tract, peritoneum, lymph node, and viscera, such as liver, spleen, and pancreas) and genitourinary (kidney and urinary tract; male and female reproductive organs) TB.

5.1. Abdominal Tuberculosis

Abdominal tuberculosis (AbTB) includes TB of the gastrointestinal tract, peritoneum, lymph nodes, and solid viscera. TB in these organs accounts for nearly 12% of all the EPTB cases [127]. AbTB is rarely primary and usually occurs by hematogenous transmission of bacilli from PTB or spread from adjacent organs with active disease, and rarely by ingestion of infected sputum. Gastrointestinal tuberculosis (GITB) includes TB of the GI tract from the esophagus to the anus, although the ileocecal disease is the most common form. The predominant symptoms of GITB are abdominal pain, fever, anorexia, nausea, vomiting, and diarrhea. Depending on the affected site, the pathological features vary from perforations, obliterations, ulceration, hypertrophy, ulcerohypertrophy, fistulae, and strictures [127].

Along with GITB, the involvement of lymph nodes or lymphadenopathy is usually observed. The most commonly involved lymph nodes are the mesenteric nodes, omental nodes, porta hepatis, the celiac axis, and the peripancreatic area. TB peritonitis is a common form of EPTB seen among patients with immunosuppression therapy, HIV infection, renal failure, and cirrhosis. As a subacute disease, TB peritonitis progress with a slow onset of symptoms, including fever, night sweats, abdominal pain, and ascites. The pathologic condition is categorized into wet ascites, fibrotic and/or dry plastic-type with a combination of one or more types usually observed. TB of the visceral organs, including the liver, spleen, and pancreas, are rarely involved in isolation; instead, they develop the disease as a secondary site and usually occur through hematogenous spread [2][128][129][130][131].

Diagnosis of AbTB is exceptionally challenging as it mimics other chronic diseases, such as malignancy, Crohn's disease, and irritable bowel syndrome. Radiological techniques, including CT or MRI, are usually performed to evaluate the extent of diseases, such as ascites, thickening of the peritoneum, lymphadenopathy, and bowel strictures [132]. Endoscopy is used to discriminate the ulcerative, hypertrophic, and ulcerative hypertrophic type of damage to the affected organs. Endoscopy, colonoscopy, laparoscopy, and ultrasound-guided aspiration and biopsy are also used to obtain samples for histopathology, AFB, and bacterial culture tests. Elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and anemia are commonly observed in blood profiling of AbTB cases [133][134][135][136][137]. In addition, ADA levels in ascitic fluid (36–40 U/L) were used to diagnose peritoneal TB with 100% sensitivity and 97% specificity (Table 2), while T-SPOT-TB indicated 90% sensitivity and 78% specificity when peritoneal fluid was used for TBP diagnosis [41][138]. Early histological changes of AbTB include caseous necrosis in an epithelioid granuloma, granulomatous lesions, lymphocyte aggregation, mucositis, and giant cell formation at the site of Mtb infection [133][135][139][140][141][142][143]. Molecular diagnosis using PCR (MBP64 or IS6110) and multiplex PCR targeting MPB64 and IS6110 regions of Mtb showed 35–65% and 75.7% sensitivity, respectively, with 100% specificity [42]. Xpert MTB/RIF has a sensitivity of 59% and specificity of 97% over MRS in an adult peritoneal fluid sample and may be used as an initial diagnostic test (Table 2) [20].

5.2. Genitourinary Tuberculosis

Genitourinary tuberculosis (GUTB) makes up to 20% of all EPTB. Usually, GUTB occurs by hematogenous spread of bacilli from the primary disease sites such as the lung and reactivation of LTBI due to immunosuppression. Kidneys are the primary organ affected in GUTB, where the disease progresses slowly and is mostly asymptomatic but can be highly destructive to the organ. TB of the kidney may even lead to renal dysfunction and renal failure. The disease usually manifests as a secondary infection in the bladder and ureter following kidneys, with extensive calcification of affected organs. Constitutional symptoms, including fever, weight loss, and sweating, are observed along with urologic symptoms, such as flank pain, pyuria, hematuria, and even urinary incontinence. There is usually no improvement after treatment with antibiotics for 5–7 days. Genital TB can affect many male genital tract organs, including the prostate, seminal vesicles, vas deferens, epididymis, Cooper glands, penis, and testicles. It typically shows tender scrotal swelling, irregular/nodular prostate, genital ulcer, and perineal sinus or fistula, leading to male infertility. TB of the female genital tract mostly affects the fallopian tubes. However, ovaries, endometrium, and peritoneum can also be affected, and symptoms are mistaken for menstrual irregularity, abdominal pain, pelvic inflammatory disease, and even infertility [144][145][146][147][148].

Chest X-ray is indicative of active PTB or healed lesions in the case of LTBI. Further imaging of affected organs using radiographic imaging, intravenous urography, ultrasonography, and CT should be performed to assess the abnormalities, fibrosis, calcification or thickening, or possible ulceration. Sterile pyuria is a classical finding in GUTB. In these cases, it is essential to culture the infecting bacilli from urine and/or biopsy samples of affected sites. The presence of AFB can also be visualized from these samples by staining. Histology studies of fine-needle aspiration or biopsy samples show classical

epithelioid cell granuloma with caseating necrosis. Compared to urine Mtb culture tests with a sensitivity and specificity of 23.3% and 100%, respectively, PCR tests performed in urine samples using Mtb IS6110, MPT64, and 16S rRNA primers had a pooled sensitivity and specificities of 88.6% and 96.5%, respectively [149]. A previous report also showed a pooled sensitivity and specificity of 87% and 91%, respectively, for Xpert MTB/RIF in detecting GUTB using urine samples [150].

6. Miliary Tuberculosis

Miliary tuberculosis (MiliTB) is a fatal form of disseminated TB developed by hematogenous spread from a primary locus. It can affect infants, young children, and older adults with predisposing co-morbidities, such as malnutrition, HIV infection, treatment with immunosuppressants, diabetes mellitus (DM), chronic kidney disease, and malignancy. The common symptoms of MiliTB are fever, malaise, anorexia, weight loss, and cough with septicemia. Specific disease symptoms are also observed depending on the organ involved and usually show cutaneous lesions (Tuberculosis cutis miliaris disseminate), choroidal tubercles, and commonly TBM. Atypical complications, including acute distress respiratory syndrome, pneumothorax, severe kidney injury, lymphadenopathy, cardiac, hepatic, and gastrointestinal manifestations, as well as immune reconstitution inflammatory syndrome, are also observed in MiliTB cases [151][152][153][154][155][156][157][158].

Diagnosis of MiliTB involves a combination of laboratory diagnosis, imaging, microbiological and molecular methods. Chest X-ray usually shows a miliary pattern, while high-resolution CT imaging specifically identifies miliary nodules, ground-glass opacities, and interlobular septal thickening. Depending on the organs involved, other diagnostic imaging, including ultrasound, MRI, Positron emission tomography-CT (PET-CT), or echocardiography, is recommended to assess the extent of organ damage. The blood profiling of MiliTB usually shows anemia, lymphopenia, pancytopenia, and elevated transaminase, bilirubin, ESR, and CRP. Sputum, bronchoalveolar lavage (BAL), or other fluids (pleural, peritoneal, pericardial, ascitic, CSF) and biopsy specimens are used for biochemical, microbiological, histopathological, and molecular testing of MiliTB, and individual sensitivity and specificity depends on the organ involved. AFB smear and bacterial culture are generally positive for mycobacteria in MiliTB. Histopathology shows caseating granuloma with necrosis. Molecular methods such as PCR or Xpert MTB/RIF, or Line Probe Assay (LiPA) can rapidly diagnose MiliTB cases. Drug-susceptibility testing is vital to confirm the susceptibility of infecting Mtb to ATDs [155][156][159][160][161][162][163][164][165]. Since HIV-positive adult blood samples showed 56% sensitivity and 94% specificity for Xpert MTB/RIF, this method is recommended by the WHO as an initial diagnostic test [20].

7. Treatment of Extrapulmonary tuberculosis

Treatment of TBM includes chemotherapy using standard anti-TB drugs (ATDs) as prescribed for PTB (Table 3). The WHO recommends 2 months of initial treatment phase with isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (ETM), followed by 10 months of INH and RIF as a standard regimen for drug-sensitive TBM cases [166][167][168][169]. The development of multidrug-resistant (MDR) Mtb strains, which are resistant to INH and RIF, is disastrous to TBM treatment. No standard or proven regimen is currently available except the one recommended by the WHO for PTB. Studies suggest using fluoroquinolones, such as levofloxacin and moxifloxacin, in addition to the standard regimen for MDR-TBM, since these drugs have good CSF penetration and are effective against MDR-strains [9]. However, these drugs have the advantage only if added early on in the treatment regimen [170][171] (Table 3). Besides the standard TB treatment, the WHO recommends using adjunctive corticosteroids, including prednisone and dexamethasone, initially as intravenous and continued as an oral treatment to reduce mortality among TBM cases (Table 1). Few studies have shown reduced patient mortality when treated with corticosteroids, which were further augmented by other drugs, such as aspirin [170][171][172]. Thus, adjunctive host-directed therapies, including corticosteroids and aspirin, should be considered for effective TBM management. In selected TBL cases, incision and drainage can be applied, and surgical intervention is rarely required. After the standard treatment, residual lymph nodes' presence is not considered a sign of recurrence or treatment failure TBL [45][173][174][175]. With OTB, systemic corticosteroids, such as oral prednisone, are recommended in the first few weeks, along with ATDs, to reduce inflammation, particularly macular edema. Topical steroids and prednisone drops can be used wherever they can alleviate the symptoms [51][176][177][178][179][180]. Paradoxical worsening of the OTB has been reported in cases with (on retroviral therapy) or without HIV infection. In these cases, new lesions developed at the same or different disease sites and worsening of existing OTB, in which case it is recommended to increase steroid dose or change the administration route (preferably systemic). The addition of immunosuppressants can alleviate the inflammation and help to resume ATDs [181][182]. Clinicians recommend using topical anti-inflammatory drugs or mucosa-protecting agents for oral tuberculosis (Table 1), depending on the case presentation seen [70][71][72]. For PLTB, the use of adjunct corticosteroid therapy is not recommended since the beneficial effects of such treatment are inconclusive. Thoracentesis could be performed in addition to chemotherapy (Table 1) to alleviate dyspnoea and reduce pleural thickening and

associated functional impairment [82][84][88][183][184]. In case of TBP, there is a proven positive effect of echocardiographic or fluoroscopic-guided needle pericardiocentesis (Table 1) to evacuate the pericardium of compressive pericardial fluid and alleviate cardiac tamponade [93][94][185][186][187]. Studies have shown neutral results with no benefits or harm in using colchicine and *M. indicus pranii* as adjuvant therapy to prevent constriction in TBP cases [188][189]. Oral or intrapericardial corticosteroids are promising yet contraindicative in HIV cases and restricted only to immunocompetent individuals [93][94][186][189][190]. Surgical excision and debridement (Table 1) are also recommended for scrofuloderma lesions, lupus vulgaris, or tuberculosis verrucosa cutis [35][102][103][191]. Chemotherapy for MSTB consists of a shorter, 6- to 9-month regimen of standard ATDs or the more extended 18-month regimen, which excludes RIF [21][22][166][167][168][169]. In case of difficulty in assessing any response and in non-complicated cases, the chemotherapy may be extended to 12 months (Table 3). Patients who do not respond effectively to chemotherapy or those with neurological deficit, cord compression, spinal instability, or kyphosis to a variable extent, particularly children, need surgical intervention (Table 1). In cold abscesses and sinus tract involvement, which are usually seen in patients with HIV, debridement and/or drainage (Table 1) is required [108][192][193][194][195]. For abdominal TB, surgery is recommended (Table 1) only when irreversible constrictions, strictures, abscesses, and fistula formation cause damage to the GI tract or other internal organs in the abdomen [128][129][196][197]. Surgical intervention is required in some GUTB cases and includes ablative surgery for partial or total nephrectomy, epididymis, urinary bladder, or fallopian tubes. Reconstruction surgery or stenting is performed in the ureters or bladder when the abnormality is irreversible. Percutaneous drainage of the affected organ is recommended when abscesses are involved (Table 1) [198][199][200][201][202]. Corticosteroids, such as prednisone, are beneficial as adjuvants for MiliTB, in which TBM, pleuritis, or pericarditis is also observed. When MiliTB co-exists with HIV infection, antiretroviral therapy should be started according to the WHO recommendations, with rifabutin replacing RIF in the ATD. Surgery is recommended (Table 1) where organ damage is irreversible [155][156][162][203][204].

Table 3. Summary of the WHO guidelines for drug-sensitive and DR EPTB treatment[$].

Resistance	Regimen	Duration	Choice of Drugs	Primary recommendations	Conditional recommendations
None	Standard chemotherapy regimen	6 months	Intensive phase – 2 months of rifampicin, isoniazid, ethambutol and pyrazinamide Continuation phase – 4 months of rifampicin and isoniazid	Continuation phase extended up to 7 months of rifampicin and isoniazid for EPTB	

				Treatment period extended up to 9 – 12 months for EPTB	
Isoniazid-resistant tuberculosis (Hr-TB)	Mono-INH regimen	6 months	Rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for 6 months	No inclusion of streptomycin or other injectable agents Drug susceptibility to fluoroquinolone by genotypic or phenotypic DST needs to be established	
MDR/RR-TB	Longer MDR regimen	Total of 18-20 months with 15-17 months after culture conversion	Combination of group A, B, C drugs to add to 4 drugs; If bedaquiline or linezolid is added, drug combination to retain 3 drugs throughout treatment	Total of 18-20 months for EPTB when culture-negative or conversion cannot be tested; Injectables used for 6- 7 months Inclusion of • levofloxacin[A] or moxifloxacin[A]* • Bedaquiline[A#] for patients aged 18 years or more. • Linezolid[A] No inclusion of kanamycin, capreomycin and clavulanic acid	Following drugs may be included • Bedaquiline[A#] may also be included in patients aged 6–17 years • Clofazimine[B#] and cycloserine[B*]/terizidone[B*] • Ethambutol[C#] • Delamanid[C#] for patients aged 3 years or more. • Pyrazinamide[C]. • Imipenem–cilastatin[C] or meropenem[C*] • Amikacin[C#] or streptomycin[C#] Following drugs may be included when bedaquiline, linezolid, clofazimine or delamanid are not used • Ethionamide[C*] or prothionamide[C*] • p-aminosalicylic acid[C#]

		9–12 months	For fluoroquinolone sensitive cases: 2 months of Linezolid–Bedaquiline-Levofloxacin-Clofazimine-Pyrazinamide, 4 months of Bedaquiline-Levofloxacin-Clofazimine-Pyrazinamide 3 months of Levofloxacin-Clofazimine-Pyrazinamide	For EPTB cases with meningitis and disseminated disease, shorter regimen should be avoided.
	Shorter all oral MDR regimen			
MDR/RR-TB		6 months		Susceptibility to fluoroquinolones needs to be established by genotypic or phenotypic DST
			For Fluoroquinolone resistant cases: 6 months of Bedaquiline-Pretomanid-Linezolid (BPaL regimen)	

[$]Therapy for EPTB recommended by the WHO guidelines for drug-susceptible and resistant TB[23-26]. Chemotherapy for EPTB is similar to PTB but the duration for EPTB should be determined by clinical or radiologic responses, mainly when culture-negative or periodic culture conversion monitoring cannot be done. For more extended MDR/RR-TB regimen, groups A (levofloxacin/moxifloxacin, bedaquiline, linezolid) B (clofazimine, cycloserine/terizidon) or C (ethambutol, delamanid, pyrazinamide, imipenem–cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, p-aminosalicylic acid) drugs are used and individual drugs are indicated in the table with a superscript [A], [B] or [C].

Hr-TB: Isoniazid (INH) resistant TB, MDR-multidrug resistant; RR-TB rifampicin resistant TB; DST-drug sensitivity test.

Notes: 1. A shorter MDR regimen is not recommended when TB meningitis or disseminated disease or HIV co-infection is indicated. 2. For meningitis * indicates the preferred choice of drug due

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