Physiopathology of Extrapulmonary Tuberculosis: A Literature Review

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Introduction: *Extrapulmonary tuberculosis (EPTB) is an infection by mycobacteria in any part of the body other than the lungs. There is information on tuberculosis infection from more than 3,000 years ago, and despite the knowledge that there is about the disease, nowadays, it is estimated that a quarter of the world population is infected and 15% of the cases are extrapulmonary.*

Aims: *This literature review aims to present the physiopathology of the most common EPTB, update and summarize the current diagnostic and therapeutic advances for the EPTB reviewed, as well as describe the physiopathological implications of coinfection with human immunodeficiency virus (HIV).*

Methods: *A literature review was performed for which PubMed, Cochrane Library, and Google Scholar databases were consulted using the following keywords: Tuberculosis, Epidemiology, Physiopathology, Diagnosis, and Therapy. Only articles published from 2016 to 2022, evaluated with a score ≥ 10 based on the Scale for the Assessment of Narrative Review Articles (SANRA) score were included, obtaining a total of 38 bibliographic sources.*

Discussion: *Depending on the system or organ affected, it is how the physiopathological process is carried through as well as how the clinical features manifest and the diagnostic approach is made. The diagnostic and therapeutic strategies of each type of EPTB have been widely studied; however, although technological innovation has contributed to the development of new diagnostic techniques, the treatment of almost all EPTB has remained the same over time, which consists of the same 6-month regimen of therapy as in pulmonary tuberculosis. Furthermore, tuberculosis treatment has been severely affected by rifampicin resistance and concomitant HIV infection.*

Conclusion: *The physiopathology of the different EPTBs is well described; nevertheless, a better understanding of how the disease spreads and develops will allow us to create new diagnostic resources and improve therapeutic targets for this disease, which still has a substantial presence worldwide.*

Keywords: *tuberculosis; epidemiology; physiopathology, diagnosis; therapy (Source: MeSH-NLM)*

INTRODUCTION

Tuberculosis (TB) is defined by the Centers for Disease, Control and Prevention (CDC) as an illness in which TB bacteria are multiplying and attacking a part of the body.[1] The principal agent causing this condition is *Mycobacterium tuberculosis* (*M. tuberculosis*); nevertheless, other five mycobacteria can cause it. These six microorganisms are grouped as the *M. tuberculosis* complex (MTC).[2] The symptoms of this pathology depend on where in the body the bacteria are growing.[1]

Even though the first written information about TB dates back to 3,300 (India) and 2,300 (China) years ago,[3] nowadays about a quarter of the world's population is infected with *M. tuberculosis*; moreover it is the second leading infectious cause of death worldwide among adults (after COVID-19).[4,5]

Although the most commonly affected system by TB is the respiratory, many other organs are susceptible to being damaged by this disease. According to the CDC, extrapulmonary TB (EPTB) is an infection by *M. tuberculosis* in any part of the body, other than the lungs.[1] EPTB occurred in 15% of all TB cases in 2016. However, there are countries like Cambodia where EPTB occurred in 34% of all TB cases and 16% of these were under the age of 15.[6]

There are identified risk factors for the acquisition of EPTB that include malnutrition, alcoholism, concomitant malignancy, use of immunosuppressive medications, and human immunodeficiency virus (HIV) co-infection.[7,8]

The most frequent sites of EPTB are the lymphatic nodes, pleura, gastrointestinal tract, central nervous

system, musculoskeletal regions, and multisystem involvement.[9] These are the EPTB types that are reviewed in this article. However, other organs and tissues can be affected such as the urinary, genital, laryngeal, pericardium, skin, and soft tissues.

JUSTIFICATION

Even though there is a lot of information and knowledge around TB, it still has a great presence in the morbidity rates all over the world and has remained the same since the beginning of the century; that is why global public health experts are constantly trying to design interventions attempting to reduce the global burden of TB. Their objective is to prevent the infection but also science is always trying to find more sensitive and efficient diagnostic tools and drugs for the ones that are already infected or cannot avoid it.[10] TB has a bigger presence in vulnerable populations with risky life situations like poverty and immunosuppression (the first killer among the HIV infected). Also, the patients who get cured of TB can suffer from long-term sequelae that affect their life quality.

This literature review aims to present the physiopathology of the most common EPTB, update, and summarize the current diagnostic and therapeutic advances for the EPTB reviewed and describe the physiopathological implications of coinfection with HIV.

METHODS

The sources of this review were consulted from the PubMed, Cochrane Library, and Google Scholar databases, with the following keywords: Tuberculosis, Epidemiology, Physiopathology, Diagnosis, and Therapy. The Free-text search terms used were: Extrapulmonary Tuberculosis, Diagnosis advances, and Therapeutic advances. The selection criteria for the cited articles were the following: systemic reviews, meta-analysis, observational studies, and bibliographic reviews published from 2016 to 2022, in English and Spanish, coming from peer-reviewed supplements, and evaluated with a score ≥ of 10 based on the Scale for the Assessment of Narrative Review Articles (SANRA). Thirty one articles, three chapters of two books, and four other bibliographic resources with adequate quality and validity were included in this review.

Epidemiology

In 2021, an estimated 10.6 million people fell ill with TB worldwide, and it was the cause of around 1.6 million deaths (187,000 deaths among HIV-positive people are included).[4]

The population at risk of TB is known to be mainly male adults. In 2021, male adults (≥ 15 years of age) represented 56.6% of the total population that developed TB, whereas females accounted for 32% and children (<15 years of age) for 11.3%.[4]

Another concern around TB that makes this disease still a public health threat is the infections caused by drug-resistant variants of *M. tuberculosis*. The drug resistance concepts considered needed for this article are defined as follows[11]:

- Mono-resistance: resistance to only one first-line anti-TB drug
- Poly-resistance: resistance to more than one first-line anti-TB drug (other than isoniazid and rifampicin)
- Multidrug resistance (MDR): resistance to isoniazid, rifampicin, and/or more
- Extensive drug resistance (XDR): Multidrug resistance plus resistance to any fluoroquinolone and one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin)
- Rifampicin resistance (RR): proven resistance to rifampicin by the usage of phenotypic or genotypic methods, with or without resistance to other anti-TB drugs.

In 2019, approximately half a million people developed RR-TB of which 78% had MDR-TB.[4] This narrows down the treatment options and compromises its response; undeniably this represents a big medical challenge.

Geographically speaking, the TB high burden countries (HBC) account for almost 90% of TB cases each year. There are three lists of HBC defined by the World Health Organization (WHO) to be used from 2021 to 2025: The TB HBC list, the TB/HIV list, and the MDR-TB list, each one accounts for 85–89% of the global burden (Fig. 1).[4–38]

Etiology

TB is caused by a group of mycobacteria called MTC. Six mycobacteria integrate this complex; however, the most relevant and responsible for most TB cases is *M. tuberculosis*.[2] The gender of *mycobacterium* to which the TB pathogen belongs is characterized by having a complex cell wall, with a lot of lipids that confer some particular qualities. Also, they have proteins associated with the cell wall that are biologically essential antigens in the cellular immune response. These proteins are extracted

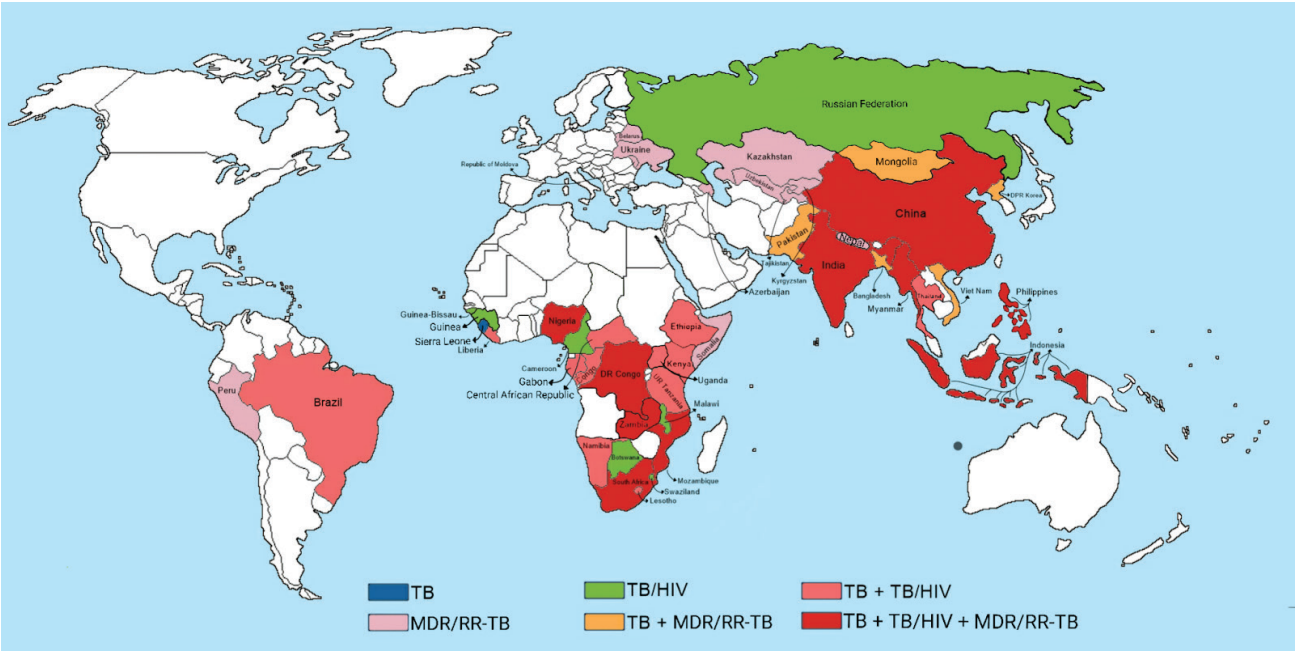

Figure 1. Geographical Distribution of Countries with a High Burden of Tuberculosis, Countries with Multidrug-Resistant/Rifampicine-Resistant Tuberculosis, and Countries with the Coexistence of TB and HIV.[38]
TB: Countries in Tuberculosis list; MDR/RR-TB: Countries in Multidrug-resistant and Rifampicine-resistant TB list; TB/HIV: Countries in Tuberculosis and Human Immunodeficiency Virus coexistence list; TB + MDR/RR-TB: Countries in Tuberculosis and Multidrug-resistant and Rifampicine-resistant TB coexistence list; TB + TB/HIV: Countries in Tuberculosis and Tuberculosis and Human Immunodeficiency Virus coexistence list; TB + TB/HIV + MDR/RR-TB: Countries in the three lists.

and partially purified, obtaining the name of purified protein derivatives (PPDs); PPDs are used as specific diagnostic skin test reagents and to measure exposure to *M. tuberculosis*.[2]

Physiopathology of Pulmonary TB (PTB)

The bacilli (inside of infected aerosols that came from an infected person) enter and penetrate the respiratory system, reaching the alveoli, and then get phagocytized by alveolar macrophages (AM), leaving the bacilli inside of a phagosome, in the AM cytosol.[12] Although *M. tuberculosis* is not an obligate intracellular bacillus, it spends most of its infection cycle within the phagocytes and the granuloma.[13]

Inside of AM, *M. tuberculosis* avoids the fusion of the phagosome with lysosomes and apoptosis, by secreting 6 kDa early secretory antigenic target (ESAT-6), and ultimately, it allows the entry of the bacillus to the cytosol.[12] Moreover, the phagosome containing the bacillus can fuse with intracellular vesicles, allowing access to nutrients, and promoting intracellular growth and multiplication.[2]

Different conditions intervene for the successful transmission of the bacillus, such as the proximity and duration of contact with a person with active TB and also the immunocompetence of the person infected with *M. tuberculosis*.[14] It should be noted that the quality and quantity of infective aerosols and pulmonary surfactant can intervene as protective factors to avoid infective capacity, as (1) not all disease patients generate the quantity and quality of aerosol necessary to be able to enter the alveolus, taking into consideration that larger particles (5 to 10 micrometers [µm]) are retained in the nose of the exposed individuals (particles <5 µm can dodge mechanical barriers and enter the pulmonary alveolus) and (2) the surfactant can destroy the lipophilic wall of *M. tuberculosis*, making it easier for AM to destroy it by phagocytizing it.[12,15]

The *M. tuberculosis* bacillus can multiplicate in a single AM up to five or six times (each replication cycle lasts 24 h), resulting in a total of 32–64 bacilli. This process generates necrosis of the AM, with the consequent exit of the bacillus to the extracellular space. Thus, these bacilli are again phagocyted both by the AMs that were

in the interstitial space and came to replace the necrotic AM, as well as by the AM of the adjacent alveoli (which arrive due to the drainage produced by the inspiration/expiration movements).[12]

The ability to host the macrophage without being lysed is one of *M. tuberculosis* pathogenesis's most important characteristics, because, in this stage of the infection, it can evade the immune system.[2,12]

As a response to infection with *M. tuberculosis* bacilli, the AM secrete tumor necrosis factor-alpha (TNF-α) and interleukin 12 (IL-12) generating recruitment of other leukocytes: T cells (TC) and natural killer cells (NKC). TC turns into helper T cells (hTC), with the consequent secretion of interferon-gamma (INF-γ). Due to INF-γ, the infected AMs are activated, which induces the fusion of phagosomes and lysosomes inside it, generating intracellular death.[2]

This process increases the inflammatory response having two possible results: 1) a necrotic mass forms (granuloma), surrounded by a compact wall of macrophages, hTC, cytotoxic T cells (CTC), and NKC with a central nucleus composed of infected AM, fused epithelioid cells (Langhans giant cells), and epithelioid cells that prevent further spread of *M. tuberculosis* but also, contain viable bacilli[2]; or 2) the balance inside of the alveoli is broken (due to the creation of exudate in the capillary that destroys the tightness of the alveolus), allowing entry of polymorphonuclear cells (PMN), enabling an energetic washing of the affected alveoli, with consequent drainage to the afferent lymphatic capillaries and lastly to the lymph nodes. At this point, *M. tuberculosis* can infect macrophages in the nodules (causing lymphadenitis) and dendritic cells.[2–10,12]

Extrapulmonary TB: Pathways of Dissemination

In general terms, EPTB occurs when the *M. tuberculosis* bacilli spread to other organs. Generally, this takes place in two ways, by the hematogenous or the lymphatic route. Nevertheless, it can spread in other ways, like through alveolar fluid that passes to the pharyngeal cavity and filters the mucosa through a small wound, causing infection in the cervical ganglia, or passing to the intestines, leading to intestinal TB.[12]

The bacilli can navigate from the lymph nodes to the efferent capillaries, which continue towards the vena cava and pass through the right atrium and ventricle to be transported back to the lung, generating new infectious foci, or reach the left atrium and ventricle, producing a systematic spread.[12]

It should be noted that the susceptibility of a system to being infected by *M. tuberculosis* is proportional to vascularization because the endothelial cells of these organs have more permeability and allow the bacilli to flow more efficiently within the tissue. That is why the most common EPTB occurs in highly vascular organs, such as bone and kidney, and happens to a minor extent in tissues with limited vascularization, such as the meninges.[12]

Lymphatic Tuberculosis

Lymphatic TB (LTB) is among the most common types of EPTB, being 30 to 50% of EPTB cases and the most frequent location is cervical lymph nodes, representing 63–77% of all LTB cases. It is caused by tuberculous mycobacteria (*M. tuberculosis)* or by nontuberculous mycobacteria, like *M. avium*, and affects most commonly children and young adults. LTB can occur due to a primary form or by the reactivation of a focus, which occurs when the balance between bacillary persistence and the immune response gets disrupted.[8,15,16]

Physiopathology of LTB

Usually, the LTB starts when, as a cause of the reactivation of a primary lung infection, TB bacilli spread by the lymphatic pathway from the mediastinal to the cervical lymph nodes (most common), causing lymphadenitis. Also, the dissemination can befall because of local extension from tuberculous infection of the tonsils or adenoids.[8,15] Nevertheless, in children, LTB can be produced by direct spread through oropharyngeal mucosa.[8]

From the regional nodes, the bacilli can proceed to proliferate through the lymphatic system to other nodes or by hematogenous spread, being able then to reach any organ (Fig. 2).[15] The clinical manifestations, diagnostic methods, and current treatment of LTB are shown in Table 1.

Pleural Tuberculosis

Tuberculosis pleural effusion (TPE) or tuberculous pleurisy is the infection of the pleura by *M. tuberculosis*[17] and is one of the most common sites of EPTB with an incidence of 3% in non-endemic areas and reaching 30% in endemic areas,[18] also pleural tuberculosis (PT) remains one of the most frequent causes of pleural exudates.[19]

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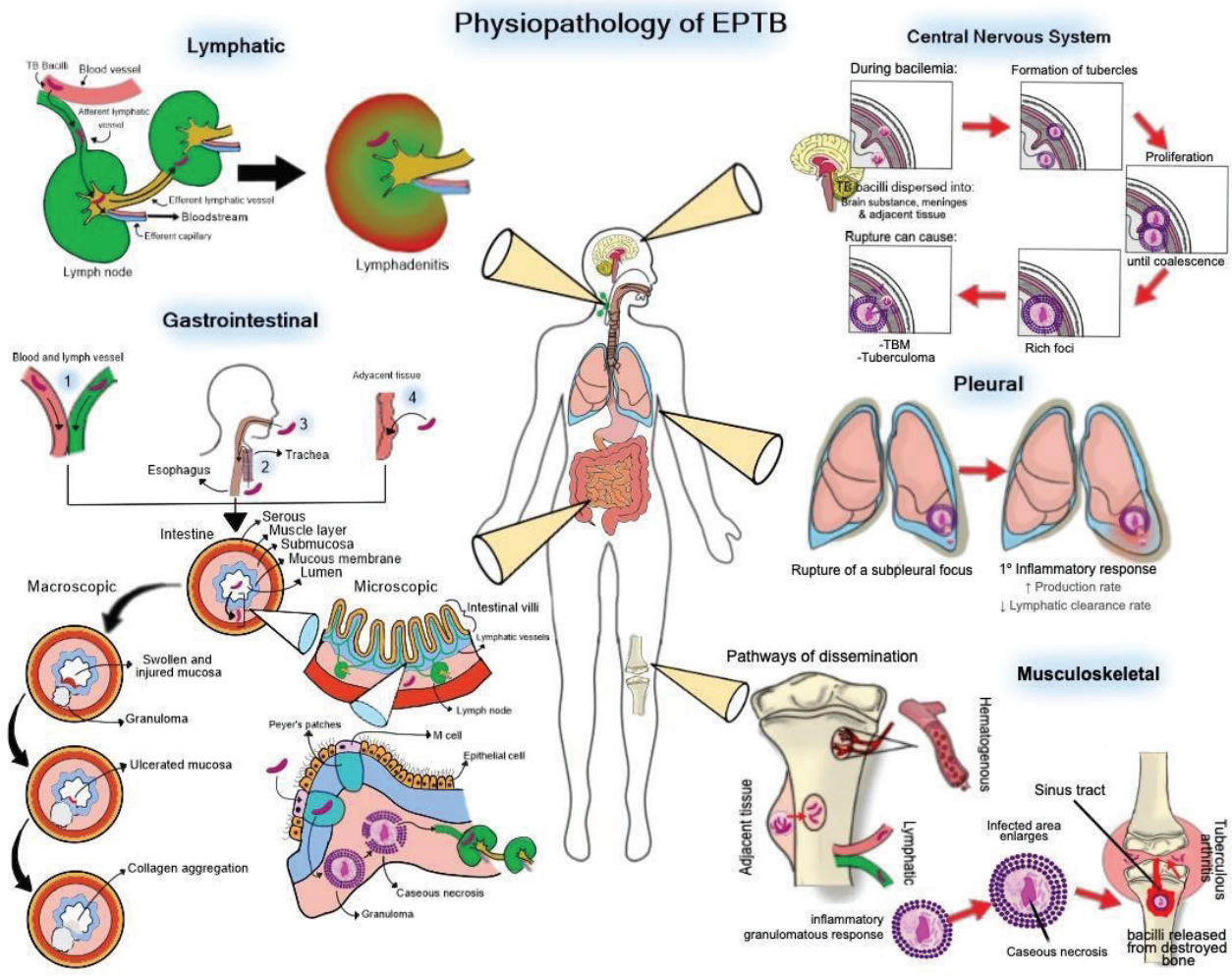

Figure 2. Physiopathology of Each EPTB.
TBM: Tuberculous meningitis.

Physiopathology of PT

PT takes place when a subpleural caseous focus ruptures and allows the *M. tuberculosis* to spread into the pleural space, causing an accumulation of fluid. The initial inflammatory response stimulates a higher rate of pleural fluid production and the same inflammatory pleuritis reduces the lymphatic rate clearance of the pleural fluid (Fig. 2).[18] The clinical manifestations, diagnostic methods, and current treatment of PT are shown in Table 1.

Gastrointestinal and Peritoneal TB

The gastrointestinal (GI) system is affected in 11–16% of EPTB cases; it represents 1–3% of all TB cases, and 6–36% of them can present concomitant PTB.[20]

Physiopathology of GITB

M. tuberculosis can spread through (1) hematogenous or lymphatic spread, (2) sputum swallowing from active pulmonary disease, (3) ingestion of infected products with *Mycobacterium bovis*, or (4) direct infection from adjacent tissue. TB bacilli capsule has many lipids that confer resistance to digestion and can intervene with an early release of the GI tract.[21] The whole GI tract can be infected, from the esophagus to the anus; however, 44–93% of cases involve the ileocecal region, being the most common location. This is explained because of specific factors of the region, including relative stasis, narrow lumen, scarce digestive activity, and the presence of microfold cells (M cells) in the lymphatic tissue that phagocytes the bacilli.[20,21] The aforementioned

Table 1. Clinical Manifestations, Diagnosis Approach, and Actual Treatments in Each Extrapulmonary TB.

Type of TB	Clinical manifestations	Diagnosis	Treatment
Lymphatic TB	**Most frequent location:** CL. Duration of lymphadenopathy: typically, 4–8 weeks. A fistula develops in 10% of cervical mycobacterial lymphadenitis. Unilateral CL presentation is more common than bilateral. 18–42% of the cases, pulmonary TB is present. **Other symptoms:** night sweats, fever, cough, and lethargy (with more incidence in HIV-positive patients).[8,16,31]	**Imaging studies:** chest Rx, neck US, CT, and MRI. **Other studies:** cytological examination, AFB staining, and molecular testing. **GS:** culture.[16,31]	**Drug-susceptible LTB (same therapy for PTB):** six-month therapy: INH, RIF; PZA, EMB for 2 months (intensive phase) followed by 4 months just with INH and RIF (continuation phase). **HIV-TB co-infection:** add ART. **MDR-TB:** a combination of second-line drugs for 9–12 months.[32]
Pleural TB	Normally acute to subacute onset. **Symptoms:** pleuritic chest pain (unilateral), cough, fever, night sweats, dyspnea, weight loss. (More to less common) Most of the effusions have a **spontaneous resolution in 2–4 months**.[18]	**Imaging studies:** chest Rx, CT scan, transthoracic US (Investigation and interventions). **Other studies:** pleural fluid analysis, sputum, and bronchoalveolar lavage, pleural biopsy.[18]	**Same therapy as used for PTB** (six-month therapy).[18]
Gastrointestinal TB	Progresses slowly and has **non-specific symptoms:** fever, abdominal pain, night sweats, anorexia, change in bowel habits (diarrhea more frequent than constipation), weight loss, nausea, vomiting, and melena. **Other manifestations:** abdominal mass often in the right lower quadrant.[22]	**Laboratory findings:** anemia and elevated ESR are characteristic, but laboratory abnormalities are not specific. **Endoscopy** is a useful diagnostic tool with the possibility of diagnostic tissue sampling for **histopathologic examination**. **Multiplex PCR:** using 3 primers (IS6110, Protein b, and MPB64) have 87.5% of sensitivity and 100% of specificity for GITB diagnosis.[20,22,33]	**Same therapy as used for PTB** (six-month therapy).[22,34] **Surgery:** indicated for the treatment of complications, such as significant bleeding, abscesses, large or drug-resistant fistulas, and intestinal obstruction.[21]
Peritoneal TB	**The presentation is non-specific:** includes ascites (most common, 73%) and can be accompanied by abdominal pain and swelling, fever, weight loss, anorexia, diarrhea, and constipation.[22,35]	**Paracentesis**: have to be done in all patients with ascites and peritoneal TB suspicion. **Laboratory findings:** normocytic anemia, monocytosis, thrombocytosis, and elevated ESR are characteristic. **Laparoscopy and histologic examination** have 98% of sensitivity.[22]	**Same therapy as used for PTB** (six-month therapy).[24]

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Table 1. Clinical Manifestations, Diagnosis Approach, and Actual Treatments in Each Extrapulmonary TB.

Type of TB		Clinical manifestations	Diagnosis	Treatment
CNS TB	Tubercu-lous meningitis	Subacute progressive febrile illness goes through three phases. **Prodrome:** malaise, low-grade fever, intermittent headache, lassitude, back or neck mild discomfort, and minor personality changes.[25] **Meningitic phase (after 2–3 weeks):** prolonged headache, vomiting, meningismus, mild confusion, different degrees of CN palsy, and long-tract signs. **(Progresses rapidly)** into a paralytic phase. **Paralytic phase:** delirium, seizures, multiple CN deficits, hemiparesis, hemiplegia, and coma.[25] If the onset illness continues untreated, within 5 to 8 weeks death commonly occurs.[25]	Proper **interpretation of the cellular characteristics and chemistries** of the CSF. **Stained smear or culture** for demonstration of mycobacteria presence in the CSF.[25]	**12 months therapy:** 2 months of RIF, INH, PZA, and EMB, followed by 10 months of RIF and INH.[7]
	Tubercu-loma	Headaches, seizures, progressive hemiplegia with or without signs of IC pressure rise. Most do not have signs of systemic infection nor symptoms of meningitis.[25]	**Clinical and epidemiological** **Other studies:** needle biopsy CT scanning with contrast enhancement.[25]	
	Arach-noiditis	More neurologic signs than infectious. Ascending or transverse radiculomyelopathy (single or multiple levels). **Symptoms:** pain, hyper or paresthesia (nerve root distribution), lower motor neuron paralysis, and sphincter incontinence (bladder or rectal). Anterior spinal artery thrombosis and infarction of the cord due to localized vasculitis.[25] Subarachnoid block (common): high CSF protein levels, pleocytosis.[25]	Increased CSF protein concentration and cell count MRI (epidural space infection).[25] Tissue biopsy and culture.[25]	
Musculoskeletal TB		Local pain is the more common, swelling, and limitation of movement present in the early stages, and advanced disease cold abscesses can be seen.[28]	**Delayed diagnosis** (indolent nature and low clinical suspicion).[28] **GS**: MRI (no pathognomonic radiographic finding) and tissue biopsy and/or culture (confirmatory).[28] Xpert MTB-RIF (81% sensitivity & 83% specificity).[27]	**The same drug regimen for PTB is appropriate.** Surgical debridement combined with chemotherapy has no proven additional benefits.[28]

Continued

Table 1. Clinical Manifestations, Diagnosis Approach, and Actual Treatments in Each Extrapulmonary TB.

Type of TB	Clinical manifestations	Diagnosis	Treatment
Disseminated TB	**The presentation is non-specific:** it includes constitutional symptoms such as fever, chills, anorexia, weight loss, fatigue, and cough. Likewise, since DTB affects different systems, the symptoms also depend on the affected organ.[30]	**Laboratory findings:** they are nonspecific. Anemia, pancytopenia, leukopenia, and DIC may occur, as well as elevated ESR and CRP. **Imaging studies:** the classic miliary pattern on chest Rx is observed in 85–90% of cases, but it is not specific for DTB. MRI can identify miliary lesions at hidden sites. **GS:** a culture of clinical samples on an agar-based medium such as Lowenstein-Jensen. The use of liquid rather than solid media reduces the diagnostic time from 6–8 weeks to 1–3.[29,36]	**Same therapy as used for PTB.**[36] Nonetheless, therapy can be individualized depending on the risk factors and clinical response of the patient.[29]

CL: Cervical Lymphadenitis; HIV: Human Immunodeficiency Virus; Rx: Radiography; US: Ultrasound; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; AFB: acid-fast bacilli; GS: Gold Standard; INH: Isoniazid; RIF: Rifampicin; PZA: Pyrazinamide; EMB: Ethambutol; ART: Antiretroviral therapy; MDR-TB: Multidrug resistance TB; ESR: Erythrocyte Sedimentation Rate; PCR: Polymerase Chain Reaction; CN: Central Nervous; CSF: Cerebral Spinal Fluid; IC: Intracranial; DIC: Disseminated intravascular coagulation; CRP: C-Reactive Protein.

enables digestion of the capsule and absorption of the bacillus.

The bacillus enters the submucosa and colonizes Peyer's patches, resulting in the inflammatory response and the formation of granulomas, these suffer caseous necrosis leaving the bacillus into the lymphatics conducts unleashing dissemination to regional nodes where more granulomas form.[21]

While this process is taking place, the granulomas grow, generating papillary elevations in the mucosa.[21] The superficial mucosa becomes swollen and injured (caused by lymphadenitis and endarteritis) producing ulcers that, when are in the healing process, can cause stenosis because of collagen aggregation. That is why there are four types of intestinal TB: Ulcerative (most common), hypertrophic, ulcero-hypertrophic (or mixed), and fibrotic (Fig. 2).[20,21]

Complications involve perforation, bleeding, fistula formation, and obstruction (caused by fibrotic stricture formation).[22]

A Great Mimicker

The GITB (and in general, all types of EPTB) is classified as 'the great mimicker' because it has been reported to mimic gastric ulcer and cancer, colorectal cancer, sarcomas, and esophageal ulcers, cancer, and tumors.[20] Also, intestinal TB has been mistaken for Crohn's disease (CD) very frequently, with a rate of misdiagnosis up to 50–70%.[20] This is why different techniques with higher diagnostic sensitivity have been studied. The meta-analysis by Jin T et al. concludes that polymerase chain reaction (PCR) has great diagnostic value, with high sensitivity to distinguish GITB from CD, yet, its specificity is low and the diagnosis of GITB should not be ruled out if the PCR is negative.[23]

Physiopathology of Peritoneal TB

The peritoneum can also be affected, generally in a hematogenous way. When this occurs, it gets thicker and hypervascular, with the consequent exudative ascites formation with protein extravasation.[22] Other routes of infection include ingestion of the bacilli that ends in mesenteric lymph nodes or adjacent spread from infected lymph nodes, genitourinary TB, or ileocecal TB.[24]

The clinical manifestations, diagnostic methods, and current treatment of GI and peritoneal TB are shown in Table 1.

Central Nervous System Tuberculosis

Central nervous system TB (CNS TB) with clinical manifestations occurs in 1–2% of all patients with an active form of TB.[25] The three most frequent forms of CNS TB are subacute or acute tuberculous meningitis (TBM), being this the most common, intracranial (IC) tuberculoma, and spinal tuberculous arachnoiditis.[25]

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Physiopathology of CNS TB

The events that lead to the neurological compromise occur when during the bacillemia, tuberculous bacilli are dispersed into the brain substance, meninges, and adjacent tissue. This results in the formation of granulomatous foci (tubercles), which continue to proliferate until they coalesce, forming a bigger caseous focus known as 'Rich foci'. These injuries, depending on their location, can rupture into the subarachnoid space producing TBM or, if the infection is contained by the proper granulomatous inflammatory reaction, then it can produce a tuberculoma (Fig. 2).[25,26]

Tuberculous arachnoiditis, as well as the IC tuberculoma, can be located at any level of the spinal cord, depending on where Rich foci's rupture happens within the cord, the meninges or even by extension from an adjacent area of spondylitis causing an inflammatory response that is usually localized and progresses in a gradual form over weeks or even months. This can lead lead to a partial to complete encapsulation of the cord producing an impingement that leads to a combination of nerve root and cord compression signs that the patients usually present.[25] The clinical manifestations, diagnostic methods, and current treatment of CNS TB are shown in Table 1.

Musculoskeletal Tuberculosis

Musculoskeletal TB (MSTB) represents approximately 10 to 15% of EPTB cases.[27] This kind of TB mostly results from a reactivation of the disease and can affect any bone, joint, or bursa, but mainly compromises large weight-bearing bones and joints, being the spine, hip, and knee the three most affected areas, accounting for 70–80% of the cases.[28] Besides bone destruction, MSTB can cause growth arrest in children, deformity, and neurological compromise when the spine is involved.[27]

The risk group varies between the different geographical regions. In countries where the disease is endemic, the affected groups are older children and young adults, but the patients are normally older persons in developed countries. Notably, information has been found about a racial risk factor, it has been detected that minorities and foreign-borns in the United States of America (USA) and the United Kingdom (UK) account for three-quarters of the MSTB cases.[28] It is important to mention that even though a correlation has been found between HIV-positive patients and the development of EPTB, there is no relation yet found between MSTB and HIV.[28]

Physiopathology of MSTB

The bone is normally involved by the hematogenous spread of *M. tuberculosis*, but it is not the only way; it can also get infected secondary to a contiguous focus of disease or due to lymphatic drainage. The initial site of infection usually is the metaphysis because they receive the richest blood supply. TB bacilli infringe on the end arteries causing endarteritis, and through the epiphysis, bone destruction. After the dissemination of the bacilli, there is an inflammatory granulomatous response and as the infected area enlarges, the central part of it becomes an area of caseating necrosis. Then, the bacilli can be released from the destroyed bone and form a sinus tract or drain into the joint space causing tuberculous arthritis (Fig. 2).[28]

If the infection is not treated properly, the progression may cause the development of 'cold' abscesses surrounding the joint or bone, which can rupture and form sinus tracts. The healing of MSTB mostly involves fibrous scar tissue formation and calcification.[28] The clinical manifestations, diagnostic methods, and current treatment of MSTB are shown in Table 1.

Disseminated Tuberculosis

By definition, disseminated TB (DTB) is the presence of ≥2 noncontiguous sites of TB infection as a consequence of lymphohematogenous dissemination of TB bacilli. This occurs due to a progression of the primary infection, the reactivation of a latent focus that spreads, or iatrogenesis (rare). The term 'miliary TB' refers to DTB that when the disease spreads by a hematogenous pathway throughout the lungs (bacillus enters the bloodstream, reaches the right heart, and enters the lungs again), presents itself with a millet-seed-like appearance on a chest x-ray.[29,30] Nowadays, miliary TB also refers to generalized and progressive forms of tuberculosis. Less than 2% of TB cases and 20% of EPTB are DTB, although it is estimated that DTB has a higher incidence, but the nonspecific clinical presentation and the lack of diagnostic tools to confirm the disease are impediments to specify the diagnosis.[29]

Physiopathology of DTB

DTB begins when an infected thrombus is generated (from a pulmonary or extrapulmonary focus as a consequence of any of the causes mentioned above) and causes embolization in the vessels of various systems, generating infection by the bacillus.[30] The clinical

manifestations, diagnostic methods, and current treatment of DTB are shown in Table 1.

HIV and Tuberculosis

The coexistence of TB and HIV is considered a syndemic. The main infectious cause of death in HIV-positive patients is tuberculosis coinfection, which is 15–22 times more likely to infect a person with this condition. Proof of this is that of the 770,000 people who died from HIV in 2019, one-third was due to TB infection. Additionally, a very alarming fact is that in 2018, 44% of people with HIV and TB coinfection did not receive treatment.[37]

Physiopathology of the Coinfection

As it is known, HIV infection decreases progressively memory and native HTC, inhibiting T helper 1 cells (Th1) and increasing T helper 2 cells (Th2), causing the acquired immunodeficiency syndrome (AIDS).[37]

The TB infection exacerbates HIV infection in several ways: (1) causes glutathione consumption, leading to oxidative stress and inflammation, allowing the proliferation of HIV-infected cells, (2) in chronic TB infection, it decreases pro-inflammatory cytokines, causing an inadequate immune response to HIV infection, (3) in acute TB infection, generates an excess of TNF-α, a major cytokine in granuloma formation that recruits macrophages and TC, causing a hot-spot for HIV-infected immune cells, and (4) in chronic TB infection, anti-inflammatory cytokines increase (due to T-cell exhaustion), increasing tunneling nanotubes that facilitate the passage of HIV from one T cell to another.[37]

CONCLUSIONS

The physiopathology of the different EPTBs is, in general, well described in the literature, however, a better understanding of why and how the disease spreads and develops will allow us to create new diagnostic resources and improve therapeutic targets for this disease, which still have a substantial presence worldwide.

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References

1. Centers for Disease Control and Prevention. TB terms. Mar 21, 2016. Available from: https://www.cdc.gov/tb/topic/basics/glossary.htm [cited 11 December 2022].
2. Murray PR, Rosenthal KS, Pfaller MA. Mycobacterium. Medical microbiology. 9th ed. Barcelona, Elsevier. 2020, pp. 226–33.
3. Barberis I, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. J Prev Med Hyg. Mar 2017; 58(1): E9–12.
4. World Health Organization. Tuberculosis. Oct 27, 2022; Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis [cited 26 October 2022].
5. Furin J, Cox H, Pai M. Tuberculosis. Lancet. Mar 2019; 393(10181): 1642–56. doi: 10.1016/S0140-6736(19)30308-3
6. Ben Ayed H, Koubaa M, Marrakchi C, et al. Extrapulmonary tuberculosis: update on the epidemiology, risk factors and prevention strategies. Int J Trop Dis. Sep 2018; 1(1): 1–6. doi: 10.23937/IJTD-2017/1710006
7. Zunt JR. Tuberculosis of the central nervous system. Continuum (Minneap Minn). Oct 2018; 24(5, Neuroinfectious Disease): 1422–38. doi: 10.1212/CON.0000000000000648
8. Rodriguez-Takeuchi SY, Renjifo ME, Medina FJ. Extrapulmonary tuberculosis: pathophysiology and imaging findings. Radiographics. Nov 2019; 39(7): 2023–37. doi: 10.1148/rg.2019190109
9. Gambhir S, Ravina M, Rangan K, Dixit M, Barai S, Bomanji J. Imaging in extrapulmonary tuberculosis. Int J Infect Dis. Mar 2017; 56: 237–47. doi: 10.1016/j.ijid.2016.11.003
10. Glaziou P, Floyd K, Raviglione MC. Global epidemiology of tuberculosis. Semin Respir Crit Care Med. Jun 2018; 39(3): 271–85. doi: 10.1055/s-0038-1651492
11. World Health Organization. Types of drug-resistant TB. Last updated unknown; Available from: https://www.who.int/teams/global-tuberculosis-programme/diagnosis-treatment/treatment-of-drug-resistant-tb/types-of-tb-drug-resistance [cited 22 November 2022].
12. Cardona PJ. Pathogenesis of tuberculosis and other mycobacteriosis. Enferm Infecc Microbiol Clin. Dec 2017; 36(1): 38–46. doi: 10.1016/j.eimc.2017.10.015
13. Huang L, Nazarova EV, Russell DG. Mycobacterium tuberculosis: bacterial fitness within the host macrophage. Microbiol Spectr. Mar 2019; 7(2): 2. doi: 10.1128/microbiolspec.BAI-0001-2019
14. Sia JK, Rengarajan J. Immunology of Mycobacterium tuberculosis Infections. Microbiol Spectr. Jul 2019; 7(4): 2. doi: 10.1128/microbiolspec.GPP3-0022-2018
15. Cataño JC, Robledo J. Tuberculous lymphadenitis and parotitis. Microbiol Spectr. Nov 2016; 4(6): 3–4. doi: 10.1128/microbiolspec.TNMI7-0008-2016
16. Gandhare A, Mahashur A. Tuberculosis of the lymph nodes: many facets, many hues. Astrocyte. Nov 2017; 4(2): 80–6. doi: 10.4103/astrocyte.astrocyte_65_17
17. Zhai K, Lu Y, Shi HZ. Tuberculous pleural effusion. J Thorac Dis. Apr 2016; 8(7): 486–94. doi: 10.21037/jtd.2016.05.87

18. Shaw JA, Diacon AH, Koegelenberg CFN. Tuberculous pleural effusion. Respirology. Jul 2019; 24(10): 962–71. doi: 10.1111/resp.13673
19. Ghumman U, Ghumman H, Nawab K, Singh A, Naeem A. Pleural Tuberculosis: a febrile presentation without respiratory symptoms. Cureus. Sep 2020; 12(9): e10643. doi: 10.7759/cureus.10643
20. Chakinala RC, Khatri AM. StatPearls. Gastrointestinal tuberculosis. Treasure Island, FL: StatPearls Publishing; 2022.
21. Choi EH, Coyle WJ. Gastrointestinal tuberculosis. Microbiol Spectr. Nov 2016; 4(6): 2–12. doi: 10.1128/microbiolspec.TNMI7-0014-2016
22. Malikowski T, Mahmood M, Smyrk T, Raffals L, Nehra V. Tuberculosis of the gastrointestinal tract and associated viscera [published correction appears in J Clin Tuberc Other Mycobact Dis 2020 Sep 09; 21: 100177]. J Clin Tuberc Other Mycobact Dis. Apr 2018; 12: 1–8. doi: 10.1016/j.jctube.2018.04.003
23. Jin T, Fei B, Zhang Y, He X. The diagnostic value of polymerase chain reaction for Mycobacterium tuberculosis to distinguish intestinal tuberculosis from crohn's disease: a meta-analysis. Saudi J Gastroenterol. Jan 2017; 23(1): 3–10. doi: 10.4103/1319-3767.199135
24. Wu DC, Averbukh LD, Wu GY. Diagnostic and therapeutic strategies for peritoneal tuberculosis: a review. J Clin Transl Hepatol. Jun 2019; 7(2): 140–8. doi: 10.14218/JCTH.2018.00062
25. Leonard JM. Central nervous system tuberculosis. Microbiol Spectr. Mar 2017 Mar; 5(2): 1–7. doi: 10.1128/microbiolspec.TNMI7-0044-2017
26. Schaller MA, Wicke F, Foerch C, Weidauer S. Central nervous system tuberculosis : etiology, clinical manifestations and neuroradiological features. Clin Neuroradiol. Sep 2018; 29(1): 3–18. doi: 10.1007/s00062-018-0726-9
27. Wen H, Li P, Ma H, Lv G. Diagnostic accuracy of Xpert MTB/RIF assay for musculoskeletal tuberculosis: a meta-analysis. Infect Drug Resist. Sep 2017; 10: 299–305. doi: 10.2147/IDR.S145843
28. Leonard MK, Blumberg HM. Musculoskeletal tuberculosis. Microbiol Spectr. Apr 2017; 5(2): 2–4. doi: 10.1128/microbiolspec.TNMI7-0046-2017
29. Khan FY. Review of literature on disseminated tuberculosis with emphasis on the focused diagnostic workup. J Family Community Med. Abr 2019; 26(2): 83–91. doi: 10.4103/jfcm.JFCM_106_18
30. Sharma SK, Mohan A. Miliary tuberculosis. Microbiol Spectr. Mar 2017; 5(2): 4, 12–14. doi: 10.1128/microbiolspec.TNMI7-0013-2016
31. Deveci HS, Kule M, Kule ZA, Habesoglu TE. Diagnostic challenges in cervical tuberculous lymphadenitis: a review. North Clin Istanb. Sep 2016; 3(2): 150–5. doi: 10.14744/nci.2016.20982
32. Qian X, Albers AE, Nguyen DTM, et al. Head and neck tuberculosis: literature review and meta-analysis. Tuberculosis (Edinb). May 2019; 116S: S78–88. doi: 10.1016/j.tube.2019.04.014
33. Malik S, Sharma K, Vaiphei K, et al. Multiplex polymerase chain reaction for diagnosis of gastrointestinal tuberculosis. JGH Open. Oct 2018; 3(1): 32–7. doi: 10.1002/jgh3.12100
34. Jullien S, Jain S, Ryan H, Ahuja V. Six-month therapy for abdominal tuberculosis. Cochrane Database Syst Rev. Nov 2016; 11(11): CD012163. doi: 10.1002/14651858.CD012163.pub2
35. Kohli M, Schiller I, Dendukuri N, et al. Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. Jan 2021; 1: CD012768. doi: 10.1002/14651858.CD012768.pub3
36. Vohra S, Dhaliwal HS. StatPearls. Miliary tuberculosis. Treasure Island, FL: StatPearls Publishing; 2022.
37. Wong K, Nguyen J, Blair L, et al. Pathogenesis of human immunodeficiency virus-mycobacterium tuberculosis co-infection. J Clin Med. Nov 2020; 9(11): 3575. doi: 10.3390/jcm9113575
38. World Health Organization. WHO global lists of high burden countries for tuberculosis (TB), TB/HIV and multidrug/rifampicin-resistant TB (MDR/RR-TB), 2021–2025: background document. 2021. Available from: https://apps.who.int/iris/handle/10665/341980 [cited 14 October 2022].