

Extrapulmonary tuberculosis: a public health problem

Tuberculosis extrapulmonar: un problema de salud pública

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Abstract

Extrapulmonary tuberculosis is defined as that case of tuberculosis clinically diagnosed and confirmed by bacteriological studies that affects tissues and organs outside the lung parenchyma. Mexico is in third place among Latin American countries in terms of the incidence of pulmonary and extrapulmonary tuberculosis. Culture methods are still the gold standard for the diagnosis of extrapulmonary tuberculosis since they identify the species and susceptibility to drugs.

Keywords: Extrapulmonary tuberculosis. Tuberculosis diagnosis. *Mycobacterium tuberculosis*.

Resumen

La tuberculosis extrapulmonar es aquella tuberculosis diagnosticada clínicamente y confirmada por estudios bacteriológicos que afecta a tejidos y órganos fuera del parénquima pulmonar. México es el tercer lugar en América Latina en incidencia de tuberculosis pulmonar y extrapulmonar. Los métodos de cultivo siguen siendo el método de referencia para el diagnóstico de tuberculosis extrapulmonar, ya que identifican la especie y la sensibilidad a los fármacos.

Palabras clave: Tuberculosis extrapulmonar. Diagnóstico de tuberculosis. *Mycobacterium tuberculosis*.

Introduction

Definition

The World Health Organization (WHO) defines extrapulmonary tuberculosis (EPTB) as clinically diagnosed tuberculosis (TB) confirmed by bacteriological studies affecting tissues and organs outside the lung parenchyma¹.

Epidemiology

Tuberculosis (TB) ranks among the ten leading causes of death across the world, with nearly 4500 deaths and 30,000 new cases reported daily. In Latin America, Mexico ranks third in the incidence rate of pulmonary TB and EPTB with 23,000 cases in 2017 (being 80% and 20% of these cases of pulmonary and extrapulmonary location, respectively). The states with the highest incidence rates were

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Baja California, Sonora, Tamaulipas, Guerrero, and Sinaloa². The age group most affected is between 15 and 45 years, with higher mortality rates seen among older adults, particularly in the presence of risk factors³. Regarding the anatomical regions of the human body affected by TB, the lung is the most common one, accounting for 80.7% of the cases, followed by EPTB (17.7%), and meningeal TB (1.6%). These infections are more predominant in men^{4,5}. A study conducted in 2017 reported that 34 out of 528 patients with suspected serositis due to TB had meningeal TB; 14, pleural TB; 8 had peritoneal TB; and 2, pericardial TB, which is indicative of a growing trend of spread and dissemination to these locations⁶.

We should mention infections due to *Mycobacterium bovis*, which accounts for 10% of all cases of EPTB. These infections are relevant due to their clinical repercussions and treatment plan⁷.

RISK FACTORS

In a study conducted at Hospital General de Mexico Dr. Eduardo Liceaga, Mexico City, Mexico, a total of 420 cases of TB were identified, 56% being pulmonary TB and 44%, EPTB. Among these cases, 60% were men and 40%, women. Regarding the EPTB cases, 63% were co-infections with the human immunodeficiency virus (HIV) or AIDS; 30% were associated with alcoholism; 30% were smokers; and 17% were associated with diabetes mellitus. We should mention that according to the WHO, individuals infected with HIV have a 30-fold higher risk of developing TB, and a higher prevalence to acquire the *Mycobacterium bovis* complex⁸. This co-infection accelerates the multiplication of HIV and leads to a rapid progression into AIDS.

PATHOPHYSIOLOGY

The bacterium *Mycobacterium tuberculosis* is mainly transmitted through the air via Flügge droplets containing the bacillus that can be inhaled by close contacts. Disease develops in 4 stages: bacillus phagocytosis, intracellular multiplication, latent phase, and active lung infection. These stages can progress into different clinical situations: disease healing, disease development, latent infection, and reactivation or reinfection⁹. *M. tuberculosis* bacilli present in the lungs or lymph nodes can undergo reactivation and

enter the systemic circulation, leading to extrapulmonary spread to multiple locations, such as the pleura, pericardium, or peritoneum⁵. In susceptible hosts, protective responses, like granuloma formation fail to restrict disease activity, thus promoting dissemination. Additionally, there is a deficit of interleukin-4 secretion that induces Toll-like receptors 2 and macrophage activation, which determines whether the *M. tuberculosis* infection will become latent or progressive¹⁰. The genes responsible for mycobacterial pathogenicity have been grouped based on their function, including envelope genes and cellular metabolic enzymes¹¹. The former synthesize proteins exposed to the bacterium's growth environment. Currently, nearly 200 genes are known, being ESAT-6 and CFP-10 the most important of all. These proteins reduce the host's innate immune response in the early stages of infection by inactivating macrophages. The cellular metabolic enzymes including *icl*, *lipF*, *fadD33*, phospholipases C, and *panC/panD* are involved in the bacterium's lipid and fatty acid metabolism for growth purposes¹¹.

The involvement of neutrophils in immunopathology is controversial to this date. It has been reported that the sera of patients with active pulmonary tuberculosis induce a series of changes in the nuclear morphology of neutrophils from healthy donors. The dominant global changes seen were apoptosis (preceded by pyknosis and karyorrhexis) and netosis (with extrusion of DNA mixed with elastase, myeloperoxidase: MPO, and histone: HIS) in some cases. All sera from patients with active pulmonary tuberculosis induced some type of change. Changes that were also common in a significant number of household contacts. Sera from healthy individuals without any contact among themselves did not produce changes or only minor changes (mainly pyknosis or nuclear inflammation, but not apoptosis or netosis). These changes were attributed to the normal short lifespan of neutrophils in vitro¹².

Ocular tuberculosis

Its incidence rate ranges from 1.4% to 18% of EPTB. It can be acquired through direct local spread, and affect the eyes and surrounding orbital tissues. Clinical signs may include exophthalmos, unilateral involvement, diplopia due to cranial nerve impairment, dacryoadenitis, abscesses, chronic blepharitis, conjunctivitis, tuberculomas, ulcers, nodular scleritis, and corneal erosions, among others¹³.

Cutaneous tuberculosis

Its incidence rate ranges from 1% to 1.5%. It can be acquired through direct inoculation and is characterized by clinical signs such as inflammatory papules, verrucous plaques, suppurative nodules, chronic ulcers, and other atypical lesions, predominantly in areas such as face, neck, and torso. There are 2 different types of cutaneous TB: endogenous, which has 3 subtypes (orificial, scrofuloderma or lupus vulgaris), and exogenous, subclassified into tuberculous chancre and verrucous cutaneous tuberculosis^{14,15}.

Intestinal tuberculosis

Abdominal TB is rare. It can occur concomitantly with diseases such as hepatic cirrhosis, carcinomatosis, sarcoma, and patients on peritoneal dialysis. It occurs due to the reactivation of latent TB disseminated through the intake of contaminated food or sputum from pulmonary TB. Symptoms are nonspecific, including chronic abdominal pain, fever, weight loss, decreased appetite, night sweats, general deterioration, malnutrition, diarrhea, and occasionally intestinal malabsorption. Ascites, fibrous bands, and adhesions between intestinal loops are often present. Additionally, complications such as intestinal obstruction, abscesses, and hemoperitoneum can occur¹⁶.

Meningeal tuberculosis

With an incidence rate ranging from 1% to 2%, it is considered the most serious dissemination, leading to significant neurological complications, sequelae, and even death. Signs are nonspecific, due to basal meningeal fibrosis and vascular swelling: overall discomfort, fatigue, anorexia, vomiting, headache, mood swings, paralysis of cranial nerves II, III, IV, VI, and VIII, strokes, seizures, and hydrocephalus due to tuberculous exudate accumulation at the cranial base. In the end stages, it causes spasticity and coma^{17,18}. Meningeal signs may be absent¹⁹.

Miliary tuberculosis

It is due to the lymphohematogenous dissemination of bacilli, which can occur during primary infection with mycobacteria or during the reactivation of a latent infection. It has multiple ways of presentation, but the involvement of multiple systems is a common

characteristic, being the lungs the organs primary damaged, followed by the liver, the spleen, and the central nervous system. It often develops in a nonspecific clinical picture, with fever and predominantly nighttime sweating, anorexia, weight loss, and cough²⁰.

Tuberculous pleural effusion

It is mainly due to the rupture of subpleural caseous focus, leading to access to pleural space, with the generation of an inflammatory reaction and increased capillary patency, and the influx of proteins, which stimulates pleural fluid formation even further. It can resolve spontaneously or progress into pleural effusion with loculations and empyema²¹.

Genitourinary tuberculosis

It is the second most common extrapulmonary localization (5% to 30% of the cases). It affects the epididymis or the prostate, commonly in men aged 30 to 50 years²². In the initial stages, it can be asymptomatic, and when it spreads into the ureter and the bladder, it causes symptoms of a urinary syndrome with sterile pyuria and microhematuria in 90% of the cases²³. Granuloma formation leads to fibrosis and ureteral stenosis, resulting in obstructive uropathy with the development of hydronephrosis²³.

Cervical tuberculous lymphadenitis

It is the most common extrapulmonary localization in adults and children²⁴. Its diagnosis is difficult to achieve due to various etiological factors causing lymph node enlargement²⁵. It often presents unilaterally, single or multiple, and is mainly located in axillary, thoracic, and abdominal lymph nodes. It can present with necrosis, fluctuate, produce ulcers, fistulas in 10% of cases, and discharge caseous material to the outside (scrofula)^{26,27}.

A study conducted at the Hospital General de México Eduardo Liceaga, Mexico City, Mexico on 87 patients with cervical lymph node tuberculosis found that 67 patients (77%) presented with unilateral lymphadenopathy (51 in the right lymphatic chain and 16 in the left one), while the remaining 20 patients showed bilateral lymphadenopathy^{24,28}.

Non-tuberculous mycobacteria commonly involved are *Mycobacterium avium*, *Mycobacterium gordonae*, and *Mycobacterium xenopi*. In studies of patients with

cervical lymphadenopathy, non-tuberculous mycobacteria have been reported in only 6.6% of the cases, identifying *Mycobacterium intracellulare*, *M. gordonae*, and *Mycobacterium fortuitum*. *Mycobacterium kumamotonense* is a slow-growing mycobacterium of the *Mycobacterium terrae* complex. The occurrence of non-tuberculous mycobacteria in HIV-positive individuals²⁷ occurs after CD4 count drops < 200 cells/mm³.

Osteoarticular tuberculosis

It represents 9% to 20% of EPTB cases. Among them, tuberculous arthritis, tuberculous osteomyelitis, and tuberculous spondylodiscitis or Pott's disease can be found (that amounts to 50% of the cases)²⁸. The latter is characterized by an infection of intervertebral discs and the adjacent vertebral bodies. It often starts on the anterior side of vertebral bodies and spreads towards the discs. In advanced cases, the infection progresses into the adjacent soft tissues causing paravertebral abscesses and damaging the posterior side of the vertebral body and spinal canal, potentially causing spinal cord compression²⁸. Symptom onset includes mechanical pain (90% of the cases) and general symptoms²⁹.

Tuberculous arthritis has been reported in 30% of the cases of bone tuberculosis, erodes the bone of the joint and destroys the adjacent cartilage. Clinical signs include chronic monoarthritis of large joints such as the coxofemoral or sacroiliac one (12-15%), followed by the knee (10%), shoulder (7%), ankle (7%), elbow (2%), and wrist (2%). Slow increase in pain, decreased range of motion, and local inflammation are common symptoms, along with other general symptoms³⁰.

Tuberculous osteomyelitis is considered rare (2% to 3% of all cases of bone TB) and predominantly affects children. Clinical signs include pain, local swelling, fever, and nighttime sweats. In later stages, it may lead to fistula formation on the skin³¹.

Peritoneal tuberculosis

It represents 25% to 50% of all cases of abdominal TB, and 0.1% to 0.7% of all cases of TB. It affects individuals between 35 and 45 years old. Three different types have been reported: 1) wet ascites with high ascitic fluid and protein content; 2) fibrotic type, characterized by intertwined adhesions of the intestines along the omentum and mesentery; and 3) dry plastic type, with inflammatory reaction, diffuse fibrous

adhesions, and nodules along the peritoneum. A total of 70% of all patients experience fever; 60%, weight loss, abdominal pain, and distension; and 15%, diarrhea, being ascites the most relevant finding³². Besides the well-known dissemination, there are two 2 different routes of infection: through the intake of infected milk or sputum, causing epithelioid tubercles in the intestinal submucosa with subsequent caseous necrosis and ulceration affecting deeper layers and infecting the peritoneum and lymphatic vessels or through direct spread from an adjacent focus, such as the fallopian tubes or an abscess in the psoas^{32,33}.

Serositis

Serous membranes are an increasingly common site of dissemination, such as the pleura, meninges, pericardium, and peritoneum, leading to an exudate and accumulation of a large amount of fluid. Although it represents < 1% of all extrapulmonary forms, its mortality rate remains high³⁴.

Diagnosis

Definitive diagnosis is achieved through positive *M. tuberculosis* culture. However, diagnosing EPTB is challenging since samples obtained from less accessible sites may have few bacilli, thus reducing sensitivity of the diagnostic test. The different diagnostic methods used to confirm the presence of tuberculosis can be divided into direct and indirect methods (Table 1).

Conventional smear microscopy has low sensitivity rates (0% to 40%) compared to cultures (30% to 80%).³⁵ The Xpert MTB/RIF test detects both pulmonary and extrapulmonary TB, as well as rifampicin resistance³⁶⁻³⁸.

A study conducted in Hospital General de Mexico Dr. Eduardo Liceaga, Mexico City, Mexico on the cost-effectiveness of diagnostic methods concluded that various forms of EPTB show that "recent" diagnostic techniques such as polymerase chain reaction and adenosine deaminase offer significant advantages (Fig. 1)³⁹⁻⁴².

Treatment

The overall objective of TB treatment is to eradicate the infection, prevent progression into active disease, improve the patient's clinical status, manage resistance exacerbation, and prevent relapse (Table 2)^{43,44}.

Table I. Direct and indirect methods for the diagnosis of tuberculosis

Direct methods	Indirect methods
Ziehl-Neelsen staining	Histopathology; it is considered the method of choice to diagnose extrapulmonary tuberculosis
Microscopy	Excision biopsy with systematic histological analysis, Ziehl-Neelsen staining, <i>M. tuberculosis</i> culture, and fine needle aspiration cytology
Culture remains the reference method to diagnose both pulmonary and extrapulmonary tuberculosis, identify species, and drug sensitivity. Notable methods include: Lowenstein-Jensen culture médium BACTEC MGIT 960 system (mycobacteria growth indicator tube) Agar-based (Middlebrook 7H10/11) culture base	Serological tests based on antibodies; cutaneous tests (Mantoux), interferon-gamma release assays, and adenosine deaminase activity. The tuberculin skin test (Mantoux) only detects the presence or absence of infection, indicating exposure to <i>M. tuberculosis</i> or latent tuberculosis. The WHO accepts only two tuberculins as standards: PPD-S PPD and PPD RT 23.
Antigen detection assays	Other indirect methods include: – Volatile organic compounds
Molecular detection: nucleic acid amplification tests such as polymerase chain reaction and automated molecular assay Xpert MTB/RIF.	– Betalactamase detection
Sensitivity and specificity are 85% and 97%, respectively. These tests play a key role in the diagnosis of meningeal tuberculosis.	
Currently, 3 methods are available, being the first 2 recommended by the WHO: – Cartridge-based nucleic acid amplification test (CB-NAAT) – Line probe assay (LPA) – Loop-mediated isothermal amplification (LAMP)	

Discussion

Back in 2018, approximately 1.5 million people died from TB, and around 10 million individuals were infected with tuberculous mycobacteria across the world. The global goal of the World Health Organization is to reduce the incidence rate of TB by 90% and mortality by 80% by 2030⁴⁵. In Mexico, its incidence rate ranks third in Latin America².

In Poland, 5487 cases of TB were reported back in 2018, 95% of which were pulmonary TB and 5%, EPTB. Among all cases, 83 patients (1.5%) showed resistance to isoniazid alone, while 48 (0.9%) showed multidrug resistance to anti-tuberculosis drugs⁴⁵. In Mexico, these figures amount to 80% for pulmonary TB and 20% for EPTB, respectively².

In Argentina, in 2019, 12,499 cases of TB were reported (a 6% higher incidence rate compared to 2018). New cases represented 93.3% of all diagnoses. Of the total number of cases, 78.6% were pulmonary TB; 11.1%, EPTB; and 10.3% lacked anatomical localization. A total of 325 cases (2.6%) of resistant TB

were reported, 43.1% of which were multidrug-resistant and 2.1% extensively drug-resistant⁴⁶.

The TB disease requires extensive attention, especially in Latin American countries, without disregarding other continents, as drug-resistant strains are becoming more prevalent, requiring molecular biology diagnostic methods only available in tertiary-level hospitals, as the one discussed in this study.

On the other hand, non-tuberculous mycobacterial disease has been on the rise in China, where a study of 607 cases of non-tuberculous mycobacteria conducted during the 2013-2016 period found that the most prevalent species were *M. avium complex* (44.5%), *Mycobacterium abscessus complex* (40.5%), *Mycobacterium kansasii* (10%), and *M. fortuitum* (2.8%)⁴⁷. In Mexico, from January 2013 through December 2014, a total of 120 patients were studied. A total of 30.8% of these patients were infected with a non-tuberculous mycobacterium. The most prevalent infections were due to *M. avium* (54.1%) and *M. intracellulare* (18.9%), while other non-tuberculous mycobacteria species accounted for 27% of the cases⁴⁴.

Table 2. Therapy for extrapulmonary tuberculosis

	6 m	Isoniazid	Including EPTB, except CNS, bone, and joints
	2 HRZE/4HR	Rifampicin	
		Pyrazinamide	
		Ethambutol	
Standard initial phase	Intensive	Isoniazid	300 mg
First-line drugs	60 doses (2 m)	Rifampicin	600 mg
For EPTB (CNS, bone, and joints)	Monday-Saturday	Pyrazinamide	1500-2000 mg
		Ethambutol	1200 mg
	Continuation Phase	Isoniazid	800 mg
	45 doses (10 m)	Rifampicin	600 mg
	3/7 days		
Retreatment	Relapse: 8 m	2HRZES/1HREZ/5H3R3E3	
	Failure	COEFAR (State Drug Resistance Committee)	
Standardized retreatment	24 m	G1: oral first-line drugs useful in TB-MDR → E, Z	
Second-line therapy		G2: injectables → S, KM, AM, CM	
		G3: fluoroquinolones → OFX, LFX, MFX	
		G4: oral second-line bacteriostatics → ETO, PTO, CS, TRD, PAS	
		G5: poor efficacy → CFX, AMX/CLV, CLR, LZD, TH, IPM/CLN, high-dose H	
Individualized retreatment	Administered for any disease location/GANAFAR (National Advisory Group on Drug Resistance)		
Second-line therapy			
EPTB	Intensive	Isoniazid	
	2 m	Rifampicin	
	Monday-Saturday	Pyrazinamide	
		Ethambutol	
	Continuation	Isoniazid	
	10 m	Rifampicin	
	3/7 d		
Meningitis and tuberculous pericarditis	6 to 8 weeks	Initial adjuvant therapy with corticosteroids (dexamethasone or prednisolone)	
Directly observed treatment	In the presence of non-compliance risk		
TB due to <i>Mycobacterium bovis</i>	Regimen extended due to up to 38% rates of pyrazinamide resistance having been reported		

AM: amikacin; AMX/CLV: amoxicillin/clavulanate; CFX: ciprofloxacin; CLR: clarithromycin; CM: capreomycin; CP: capreomycin; CS: cycloserine; E: ethambutol; ETO: ethionamide; H: isoniazid; IPM/CLN: imipenem/cilastatin; KM: kanamycin; LFX: levofloxacin; LZD: linezolid; MDR: multidrug-resistant; MFX: moxifloxacin; OFX: ofloxacin; PAS: para-aminosalicylic acid; PTO: prothionamide; R: rifampicin; S: streptomycin; CNS: central nervous system; TB: tuberculosis; EPTB: extrapulmonary tuberculosis; TH: thioacetazone; TRD: terizidone; Z: pyrazinamide

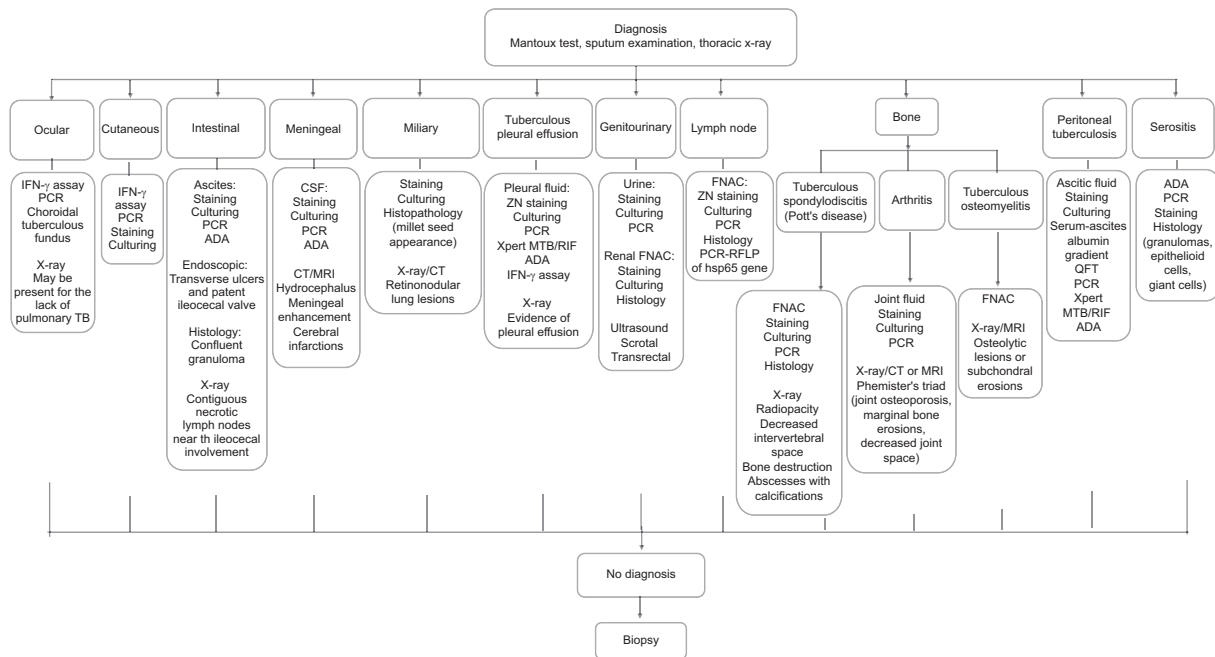


Figure 1. Diagnostic methods to identify different types of extrapulmonary tuberculosis. ADA: adenosine deaminase; CSF: cerebrospinal fluid; CT: computed tomography; FNAC: fine needle aspiration cytology; INF γ : interferon-gamma; MRI: magnetic resonance imaging; QFT: QuantiFERON; RFLP: restriction fragment length polymorphism; Rx: x-ray; TB: tuberculosis; USG: ultrasonography; ZN: Ziehl-Neelsen staining.

Conclusions

Although the WHO strategy has been established in recent years to reduce the mortality and incidence rates associated with TB, we'll only see this reduction when a more accurate number of diagnosed patients becomes available and when primary and secondary health care centers, upon suspicion of TB, promptly refer cases to tertiary-level hospitals. These forms of tuberculosis are challenging because it is difficult to achieve a definitive diagnosis, because both the clinical signs and the imaging modalities can be nonspecific.

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Conflicts of interest

None reported.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this study.

Patients' data protection. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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