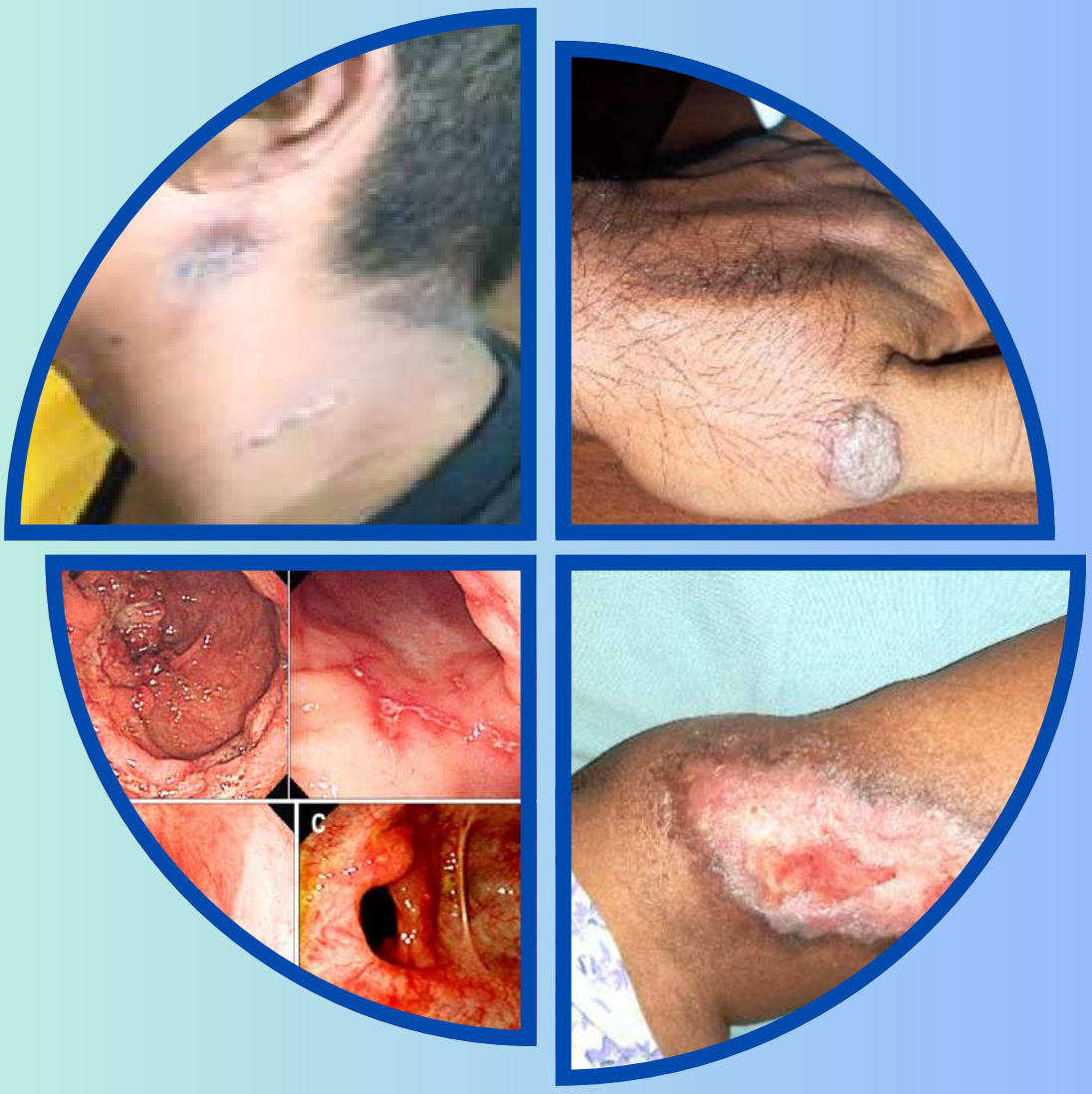
National Guideline on Management of Extra Pulmonary Tuberculosis 2024



National Programme for Tuberculosis Control and Chest Diseases (NPTCCD)

National Guideline on Management of Extra Pulmonary Tuberculosis 2024

National Programme for Tuberculosis Control and Chest Diseases

2024

MESSAGE FROM THE DIRECTOR GENERAL OF HEALTH SERVICES

In line with the Global End TB Strategy and the Sustainable Development Goals (SDGs), Sri Lanka is pledged to End TB by 2035 through strengthening active case finding, standard management and enhancing preventive measures.

Nearly one fourth of the TB patients are having extra pulmonary TB. The National Programme for Tuberculosis Control and Chest Diseases (NPTCCD), as the main focal point at the national level responsible for controlling the TB burden in the country, has taken the initiative of updating the Guideline on management of Extra Pulmonary Tuberculosis.

The revised guideline is updated with evidence and knowledge in TB control and management through incorporating the newly developed guidelines and other documents. This updated edition is a result of the joint venture of all stakeholders in TB care.

The financial support provided by the World Health Organization to bring together experts from various fields to successfully carry out technical work was a pillar of strength to the NPTCCD.

I hope this manual will provide guidance to all health care professionals involved in TB patient care management, prevention and to support us in the pathway of elimination of TB in Sri Lanka.

Dr. Asela Gunawardene

Director General of Health Services

Ministry of Health

MESSAGE FROM THE DEPUTY DIRECTOR GENERAL (PUBLIC HEALTH SERVICES) II

TB is the leading infectious disease for deaths globally as well as in Sri Lanka, accounting to around 700 reported deaths annually. Delay in diagnosis is one of the main reasons for poor disease outcome. Extra Pulmonary TB poses a greater challenge when it comes to diagnosis, as the symptoms could vary depending on the affected body part. Therefore, a greater degree of suspicion is needed in timely diagnosis and management to prevent poor outcomes.

As one fourth of TB case load is reported with EPTB, it is essential to have updated guidelines for the clinicians to efficiently diagnose these patients. TB being able to affect almost all parts of the body, EPTB poses a difficulty in diagnosis, unless clinical suspicion and meticulous investigation procedure is carried out. Also, the diagnostic procedures available are advancing rapidly. Hence, updating the existing guideline, including new knowledge on EPTB is an urgent need. Therefore, the National Programme for Tuberculosis Control and Chest Diseases (NPTCCD) took initiatives to revise and update the previous guideline published in 2013.

Contributions made by the College of Pulmonologists, College of Pediatricians and other professional colleges, Consultant Community Physicians, members of the Technical Support Group to the NPTCCD, District Tuberculosis Control Officers, and Medical Officers of NPTCCD have resulted in a comprehensive EPTB guideline.

I extend my well wishes to all the contributors in this venture and hope this guideline would pave the way in achieving end TB goals in the near future.

Dr. S.M. Arnold

Deputy Director General (Public Health Services) II

Ministry of Health

PREFACE

Sri Lanka is classified as a low burden country for tuberculosis with around 14000 estimated cases per year. The annual detection of tuberculosis cases within the country is approximately 10,000, of which about 2500 cases are extrapulmonary tuberculosis (EPTB) patients. While annually around 75% of the notified TB patients have TB in lungs, the rest of the 25% have TB in other parts of the body. This portion of EPTB patients also have to be identified and treated in reaching end TB targets in the near future.

The new guideline includes new chapters and comprehensive information on diagnosis of EPTB in each body organ. The chapters are based on latest guidelines developed by World Health Organization and the standard guidelines followed by the respective clinical fields at the international level.

I would like to extend my sincere gratitude to the Sri Lanka College of Pulmonologists for their collaborative effort with NPTCCD to revise this guideline. I also wish to express my heartfelt appreciation to all the other consultants representing the respective colleges for their unwavering commitment. This significant accomplishment would not have been possible without their dedication to seeing this project through, despite their busy schedule.

It is my hope that this guideline will serve as an essential resource for clinicians, providing standardized and quality-assured management for patients with EPTB.

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ABBREVIATIONS

ACTH	Adreno corticotropic hormone
ADA	Adenosine deaminase
AFB	Acid Fast Bacilli
ALT	Alanine aminotransferase
ART	Anti-Retroviral Therapy
AST	Aspartate aminotransferase
ATT	Anti Tuberculosis Treatment
BCG	Bacillus Calmette Guérin
BHIVA	British HIV Association
BPF	Bronchopleural Fistula
CB-NAAT	Cartridge Based Nucleic Acid Amplification Test
CD4	CD4 T lymphocyte
CFU/ml	Colony Forming Units per milliliter
CNS	Central Nervous System
CNS TB	Central Nervous System Tuberculosis
CRF	Chronic Renal Failure
CSF	Cerebro-Spinal Fluid
CT	Computed Tomography
CT IVU	CT Intra Venous Urography
CXR	Chest Xray
DST	Drug Susceptibility Testing
EPTB	Extra Pulmonary Tuberculosis
ESR	Erythrocyte sedimentation rate
FDC	Fixed dose combinations
FLQ	Fluoroquinolones
FNA	Fine-Needle Aspirates
FNAB	Fine-needle aspiration biopsy
FNAC	Fine Needle Aspirate Cytology

GCS	Glasgow Coma Scale
GFR	Glomerular Filtration Rate
GUTB	Genito Urinary Tuberculosis
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
HRCT	High-resolution computed tomography
HSG	Hysterosalpingography
IATA	International Air Transport Association
IC	Intercostals
ICAM-1	Intercellular adhesion molecule-1
ICI	Immune Checkpoint Inhibitor
ICP	Intra Cranial Pressure
IFN-γ	Interferon-gamma
IGRA	Interferon Gamma Release Assay
IL-12	Interleukin-12
INH	Isoniazid
IRIS	Immune reconstitution inflammatory syndrome
LAM	Loop-mediated isothermal amplification
LDH	Lactate dehydrogenase
LETM	Longitudinal extensive transverse myelitis
LF-LAM	Lateral Flow urine lipoarabinomannan assay
LJ	Lowenstein-Jensen
LTBI	Latent Tuberculous Infection
MAI	*M. avium- intracellulare*
MDCT	Multi Detector Computed Tomography
MOTT	Mycobacteria Other Than Tuberculosis
MRI	Magnetic resonance imaging
MSMD	Mendelian susceptibility to mycobacterial diseases
MTB	Mycobacterium Tuberculosis

MTBC	*Mycobacterium tuberculosis* complex
NPTCCD	National Programme for tuberculosis Control and Chest Diseases
NTM	Non-Tuberculous Mycobacteria
OTB	Ocular tuberculosis
PCR	Polymerase Chain Reaction
PPE	Personal Protective Equipment
PR	Paradoxical reaction
PTB	Pulmonary Tuberculosis
PUO	Pyrexia of unknown origin
RIF	Resistance to rifampin
SAAG	Serum-ascites albumin gradient
SIADH	Syndrome of inappropriate anti-diuretic hormone
SLID	Second-line injectable drugs
TB	Tuberculosis
TBM	Tuberculous meningitis
TBP	TB Pericarditis
TBPE	Tuberculous pleural effusions
tPA	Tissue plasminogen activator
TTB	Tuberculous trochanteric bursitis
TST	Tuberculin skin test
URT-TB	Upper respiratory tract in tuberculosis
USS	Ultra Sound Scan
VATs	Video-assisted Thoracoscopic Surgeries
JVP	Jugular Venous Pressure

Chapter 1: INTRODUCTION

The National Programme for tuberculosis Control and Chest Diseases (NPTCCD) has developed the first guidelines on diagnosis and treatment of Extra Pulmonary Tuberculosis (EPTB) in 2013. However, a considerable development in the fields of diagnosis and management of EPTB has occurred with the changing global evidences and therefore, the knowledge and the skills of the clinicians should be updated by incorporating the new evidences in a form of revised guidelines.

1.1 Epidemiology of TB and EPTB

Tuberculosis (TB) is an infectious disease caused by the bacillus- Mycobacterium tuberculosis (MTB) and occasionally by *Mycobacterium bovis* and *Mycobacterium africanum.* The disease commonly affects the lungs but can affect any other organ in the body except nails and hair. Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree while EPTB refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

TB remains as the second leading cause of death (after COVID-19) in the world since 2020. In 2021, an estimated 10.6 million people got infected and approximately 1.6 million people died due to TB, worldwide. The South East Asia Region shoulders the highest TB burden (43% in 2021). Sri Lanka reported around 8000 to 9000 TB cases prior to the year 2020, which dropped up to 7258 and 6771 in the year 2020 and 2021 respectively due to Covid19 pandemic. Total number of TB cases picked up in the year 2022 notifying 8342 total TB cases.

Majority (70%) of TB patients are PTB, EPTB contributed to 25% - 27% of total TB cases since 2013 which reduced to 23% in 2022. Notification rate of EPTB has been reduced by 42% since 2013 (Table 1). There is an important relationship between Human Immunodeficiency Virus (HIV) and EPTB. As per the global evidence, EPTB constitutes 40–68% of all TB cases among HIV-infected patients, whereas only 15–20% of all TB cases in immune-competent patients present as EPTB. Initiation of Anti-Retroviral Therapy (ART) for HIV patients and reducing trend of HIV and overall reduction in infectious TB could be the probable reasons for the reduction in EPTB cases amid advancement in diagnostic facilities. Among the commonest sites for EPTB, Tuberculous peripheral lymphadenopathy (TB adenitis), Tuberculous pleurisy

and spinal TB are the commonest in respective order. However, compared to 2013, 2022 saw a reduction in reported cases of TB adenitis and TB pleurisy where as an increase notification in TB spine.

Table 1: Proportion of EPTB out of all TB cases and EPTB notification rate 2013-2022

Year	Total TB patients	Total EPTB patients	Percentage (%) of EPTB patients	Notification rate of EPTB patients/100,000 population
2013	9496	2463	25.9	12.1
2014	9473	2568	27.1	12.5
2015	9575	2699	28.2	12.9
2016	8886	2525	28.4	11.9
2017	8511	2228	26.2	10.5
2018	8856	2431	27.5	11.3
2019	8434	2123	25.2	9.8
2020	7258	1928	26.6	8.8
2021	6771	1833	27.1	8.3
2022	8342	1995	23.9	7.0

(Source: TB Annual Report: NPTCCD)

1.2 Transmission of TB

TB is an airborne infection. When a patient with infectious pulmonary TB coughs, sneezes or laughs, bacilli are expelled into the air in the form of tiny droplets. These droplets dry up rapidly to form droplet nuclei and may remain suspended in the air for several hours. When a healthy person inhales these droplet nuclei containing the tubercle bacilli, he/she may become infected. Adequate ventilation removes and dilutes these droplet nuclei, but they can survive in the dark ill-ventilated spaces for several days.

Certain procedures, for example, bronchoscopy, sputum induction, autopsy and even irrigation or other manipulation of tuberculous abscesses, may also produce infectious aerosols. The droplets have an extremely slow settling rate (0.5 mm per second or less), which permits their transport by air currents for significant distances from the source case. For practical purposes, only the droplet nuclei in the size range 1 to 5 microns reach the terminal air spaces or alveoli; each is understood to contain only a few bacteria.

1.3 Risk of infection

An individual's risk of infection depends on the extent of exposure to an infectious source and susceptibility of the individual to infection. The risk of infection is therefore high in a person who has close, prolonged exposure to a person with sputum smear positive pulmonary TB. An untreated sputum positive patient has the potential risk of infecting 10-15 persons per year. The risk of transmission of infection from EPTB is lower though laryngeal TB are infectious.

1.4 TB infection

TB develops in two stages. The first stage occurs when the tubercle bacilli enter the body of an individual but remain dormant without causing disease. This is called Latent Tuberculous Infection (LTBI). LTBI is defined as a state of persistent immune response to stimulation by MTB antigens with no evidence of clinically manifested active TB. The only sign of TB infection is a positive reaction to the tuberculin skin test (TST) or Interferon Gamma Release Assay (IGRA). Persons with latent TB infection are not infectious and cannot spread TB infection to others**.**

1.5 progression of infection to active TB disease

Once infected with MTB, a person probably remains infected for rest of the life. Approximately 10% of people infected with bacillus but not suffering from any other concomitant immunosuppressive condition will develop the active disease during their lifetime.

The majority (90%) will not develop the disease and the only evidence of infection in these people may be a positive TST. The organisms may remain dormant within the body and the disease can develop at any time. The chance of developing the disease is greatest within the first two years and lessens as time goes by, but the risk probably remains for the lifetime. Weakening of the immune system can cause rapid progress of the infection to the disease status. Examples are HIV infection, diabetes, chronic kidney disease, malnutrition, prolonged steroid therapy, chronic alcoholism, and malignancies.

1.6 Pathogenesis

1.6.1 Primary infection

Primary infection occurs on first exposure of a person to the tubercle bacilli. Once the tubercle bacilli enter the respiratory tract through inhalation, organisms reach the alveoli of the lungs where they are engulfed by macrophages and presented to lymphocytes. This leads to an immune reaction against MTB which results in sub pleural Ghon focus with enlargement of the draining lymph nodes 4–6 weeks after primary infection. Ghon focus and the enlarged draining nodes comprise primary complex. In most cases the immune response is sufficient to stop the multiplication of bacilli and to prevent the development of the disease. The primary lesion may heal by fibrosis or by calcification. A positive TST may be the only evidence of infection. In a few cases primary infection progresses and leads to complications of primary infection. Complications of primary infection can manifest as early complications such as pleural effusion, miliary TB, TB meningitis or late complications such as bone TB, renal TB etc.

1.6.2 Post-primary TB

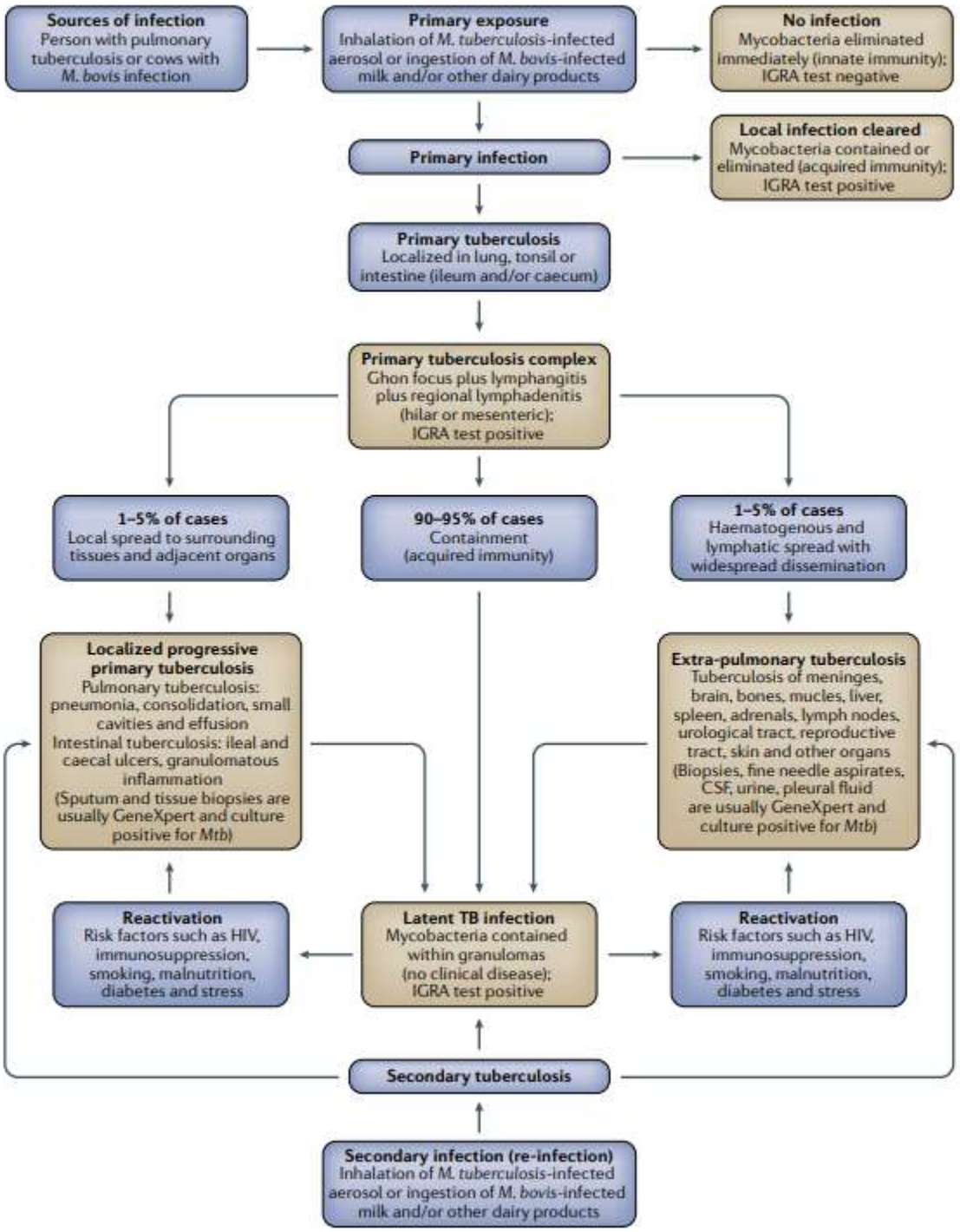
Post primary TB occurs after a latent period of months or years after the primary infection. It may occur either by endogenous reactivation of the latent primary infection or by exogenous re-infection with TB bacilli. Site of post primary TB is usually the lungs and results in lung cavitation, fibrosis and patchy consolidation. They are the patients who may become sputum positive thus contributing to spread of the disease.

1.7 Common symptoms of pulmonary TB

1.7.1 Respiratory symptoms:

- Cough - usually more than two weeks. However, in immune-compromised and in the presence of any other risk factor, cough of any duration should lead to screening for TB.
- Shortness of breath
- Chest pain
- Hemoptysis (blood-stained sputum)

Figure 1: Schematic representation of pathogenesis and natural history of MTB infection



1.7.2 Constitutional symptoms:

- Fever and night sweats
- Loss of appetite
- Loss of weight or failure to gain weight in case of children
- Tiredness (fatigue)

1.8 Symptoms of extra pulmonary TB (EPTB):

EPTB symptoms usually depend on the organ involved. Patients may present with constitutional features of the disease such as, fever, night sweats, loss of weight and loss of appetite or symptoms related to the affected system (e.g., neurological symptoms when nervous system is affected) or local symptoms like swelling (most commonly due to lymph nodes enlargement) related to the site of the disease.

1.9 References

1. Annual report on TB 2021. https://www.nptccd.health.gov.lk/downloads/

Chapter 2: CLASSIFICATION OF EXTRA PULMONARY TB

A case of TB is defined as "A patient in whom TB has been either bacteriologically confirmed in laboratory or clinically diagnosed based on a clinician's decision taking into account clinical picture, results of other investigations and risk factors".

2.1 Classification based on anatomical site of the disease

- Pulmonary TB (PTB)

  Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree with or without the involvement of any other organs in the body.

- Extra pulmonary TB (EPTB)

  Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lung parenchyma or tracheobronchial tree, e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, bones and joints, meninges.

In this chapter, general classification for TB is discussed with relevance to EPTB.

Presumptive EPTB patient

A presumptive EPTB patient is an individual with symptoms and signs suggestive of EPTB in a body part, which warrants further investigation.

2.2 Classification based on bacteriological status

According to WHO guidelines, EPTB refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).

- Bacteriologically confirmed TB

Any EPTB patient positive for AFB by microscopy, culture or MTB/RIF can be considered a bacteriologically confirmed EPTB patient.

- Clinically diagnosed TB

A patient who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician and after consultation with a Consultant Respiratory Physician and decided to treat the patient a with a full course of TB treatment.

An EPTB patient in whom microbiological tests are negative, however, there's strong clinical suspicion and other evidence such as histological findings, compatible imaging findings, other ancillary diagnostic tests or response to anti TB treatment, suggestive of EPTB can be considered as a clinically diagnosed EPTB patient.

A presumptive EPTB patient in whom Anti Tuberculosis Treatment (ATT) was commenced empirically without microbiological testing, with response to anti TB treatment, can also be taken under this category.

However, all above categories are separately categories as EPTB patients for management and recording and reporting purposes.

2.3 Classification based on history of previous TB treatment

1.) New patients

A patient who has never taken treatment for TB

OR

A patient who has taken anti-TB drugs for less than one month

New patients may have positive or negative bacteriology and this is common to both the PTB and EPTB patients.

2.) Previously treated patients

Patients, who have received one month or more of anti-TB drugs in the past are classified under this category. They are further classified by the outcome of their most recent course of treatment.

a.) Relapse

Patients who have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB.

For EPTB patients, any patient after completing the full course of anti TB treatment, presenting again with symptoms and signs suggestive of TB, with or without evidence of microbiological evidence of persisting *M. TB* can be considered a relapse.

b.) Treatment after failure

Patients who have previously been treated for TB and whose treatment failed during or at the end of their most recent course of TB treatment.

In EPTB patients, this may be indicated by compatible imaging findings and other ancillary diagnostic tests or response to anti TB treatment.

c.) Treatment after loss to follow-up

Patients who have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment (These were previously known as treatment after default patients).

d.) Other previously treated patients

Patients who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

3.) Patients with unknown previous TB treatment history

Patients who do not fit into any of the categories listed above.

e.g., Patients treated outside NTP, patients returning from abroad

2.4 Classification based on HIV status

HIV status should be tested in all TB patients including EPTB patients.

- **HIV-positive TB patient** refers to any TB patient who has a positive result from HIV confirmatory test.
- **HIV-negative TB patient** refers to any TB patient who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly.

- **HIV status unknown TB patient** refers to any TB patient who has no result of HIV testing. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

2.5 Treatment outcomes for TB patients

All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome from this list at the end of their treatment.

1.) Treatment completed

A patient who completed treatment as recommended by the national policy whose outcome does not meet the definition for cure or treatment failure. According to the existing national policy, a patient who completed treatment without evidence of failure but with no record to show that smear or culture results in the last month of treatment and on at least one previous occasion is negative, either because tests were not done or because results are unavailable falls in to this category. This includes patients who were bacteriologically negative at the beginning and remained so.

For EPTB patients this is the most desired outcome once they complete the treatment provided there is no evidence or treatment failure. A TB patient who has clinical and radiological evidence of resolution of active TB at the end of ATT will also fall in to this category.

2.) Treatment failed

A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy.

Reasons for the change include:

- No clinical response and/or no bacteriological response
- Adverse drug reactions or
- Evidence of additional drug resistance to medicines in the regimen.

3.) Died

A patient who died for any reason before starting treatment or during the course of treatment.

4.) Loss to follow up

A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

5.) Not evaluated

A patient for whom no treatment outcome is assigned. This includes cases for whom the treatment outcome is unknown to the reporting clinic.

- Treatment success

Traditionally, this is the sum of all patients cured and treatment completed. This would include all EPTB patients in whom treatment was completed.

2.6 Drug resistance in EPTB patients

Measuring drug resistance among EPTB patients is limited as most patients are diagnosed clinically. However, in patients with bacteriological isolates, culture and DST can be performed. Reported drug resistance among EPTB patients can be classified as same for the PTB patients (Refer National Guidelines for Programmatic management of Drug-Resistant TB, 2021).

2.7 References

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Chapter 3: DIAGNOSIS

3.1 Diagnostic Considerations

EPTB affects almost all organs of the body and hence signs and symptoms vary accordingly. Therefore, diagnosis of EPTB is a challenge especially with low level of clinical suspicion and non-specific clinical features.

A high index of suspicion is of paramount importance for the rapid diagnosis of EPTB. Delay in EPTB diagnosis may be related to the often nonspecific (e.g., fever, night sweats, weight loss) or organ-specific presentation compounded by the absence of an abnormal chest radiograph or positive sputum samples. When evaluating at-risk patients with fever of unknown origin, with fever and site-specific signs and symptoms of patients with biopsy-proven granulomatous inflammation, appropriate steps should be taken to secure the diagnosis of TB and thereby reduce morbidity and death.

With a diagnosis of EPTB established, confirmation of HIV status is imperative. Whenever practical, every effort should be made to obtain clinical samples for both mycobacteriological [Acid Fast Bacilli (AFB)] smear and culture and molecular tests.

Biopsy material for mycobacterial culture should be submitted fresh or in a small amount of sterile saline.

Histopathologic sample requires the specimen to be placed in formalin, which destroys the mycobacteria and prevents further attempts to culture.

3.2 Investigations

In all cases of suspected EPTB, diagnosis depends on the organ/system involvement. In such patients, every attempt must be looked for co-existing PTB.

In suspected EPTB patients every attempt must be made to look for co-existing PTB

3.2.1 The Acid-Fast smear and microscopy

Bacteriological confirmation should be attempted wherever possible since other diseases could mimic EPTB. The early and rapid diagnosis of TB can be made by positive AFB smear in both PTB and EPTB specimens. Overall, smears have a reported sensitivity of 22% - 65%.

Diagnostic yield of EPTB specimen from direct smear depends on standard of laboratory procedure and expertise. Since, EPTB samples are paucibacillary, sensitivity is further low in AFB smears.

3.2.2 Mycobacterial culture

Mycobacterial culture, as the gold standard for diagnosis, is highly recommended for laboratory confirmation of TB regardless of AFB smear or nucleic acid amplification results. Since greater proportion of EPTB cases are negative for AFB, culture remains as an important part of EPTB diagnostics.

The specimen can be cultured in solid or liquid media (BACTEC Mycobacterium Growth Indicator Tube –MGIT 960 automated system). However, culture result may take 2-6 weeks depending on the culture method employed. Liquid culture which is more sensitive and rapid, can provide results in as early as two weeks. Conventional solid culture on **Lowenstein-Jensen (LJ)** media, may take 4-6 weeks. Decision to treat will have to be taken on clinical and available other supportive evidences and culture may provide retrospective confirmation of diagnosis. In addition, **Drug Susceptibility Testing (DST)** and further testing can be performed based on the culture isolates.

3.2.3 Cartridge Based Nucleic Acid Amplification Test (CB-NAAT)

Cartridge Based Nucleic Acid Amplification Test (CB- NAAT), is an automated molecular technique which amplifies target sequences of DNA from the *M. tuberculosis* organism. CB-NAATs are expensive tests but have several important advantages. They are rapid with excellent sensitivity and specificity.

Xpert MTB/RIF Ultra is a WHO recommended, cartridge based, semi quantitative, nested real-time polymerase chain reaction (PCR) assay that simultaneously detects TB and rifampicin resistance within hours. This assay is revolutionizing TB control by contributing to the rapid diagnosis of TB disease and drug resistance.

Xpert MTB/RIF Ultra should be used when indicated as an initial diagnostic test or as an additional test to conventional smear microscopy, culture and cytology.

1. Xpert MTB/RIF assay - The Xpert MTB/RIF test simultaneously detects *Mycobacterium tuberculosis* complex (MTBC) and resistance to rifampin (RIF) in less than 2 hours. The

analytical limit of detection of the Xpert MTB/RIF assay is reported to be 131 **CFU**/ml (Colony Forming Units per milliliter) of specimen, based on spiked-sputum studies.

2. Xpert MTB/RIF Ultra assay – Previously used Xpert MTB/RIF has improved sensitivity in the detection of TB and rifampicin resistance in less than 80 minutes. Currently in use Xpert **Ultra** detects **lower** concentrations of MTBC (16 **CFU**/ml). Trace results are common with the use of Xpert Ultra in paucibacillary specimens. WHO recommends people being evaluated for EPTB, the "M. tuberculosis complex detected trace" Ultra result is considered as bacteriological confirmation of TB.

3. Xpert MTB/XDR assay- allows fast molecular DST by detecting mutations associated with resistance towards Isoniazid (INH), fluoroquinolones (FLQ), second-line injectable drugs (SLID) (amikacin, kanamycin, capreomycin) and ethionamide in a single test. This test can be performed on patients in whom rifampicin resistance was detected by Xpert MTB/RIF assay or Xpert MTB/RIF Ultra assay.

Table 2: Comparison between Xpert MTB/RIF Ultra Assay and Xpert MTB/XDR assay

	Xpert MTB/RIF Ultra Assay	**Xpert MTB/XDR assay**
Indication	MTB detection and Rifampicin resistance (RR) detection	For patients with known RR in order to detect further drug resistance
MTB detection	Yes	Yes
Rifampicin Resistance detection	Yes	No
Resistance detection of INH, Fluoroquinolone, Amikacin, Kanamycin, Capreomycin, Ethionamide	No	Yes
Mycobacteria Other Than Tuberculosis (MOTT) detection	No	No

Table 3: Investigations in TB

1. Microbiological

- The acid-fast smear microscopy
- CB-NAAT
- Mycobacterial culture

2. Biochemical

- ESR
- CRP
- HIV
- FBC
- FBS
- Liver profile
- Renal profile
- **IGRA**
- **TST**

4. Radiological tests

- Chest X Ray (CXR)
- X Ray other sites
- USS
- Echocardiogram
- Computerized Tomography (CT)
- Magnetic resornance imaging (MRI)

5. Histopathology

6. Invasive investigations

- True cut biopsies
- Bronchoscopy
- Thoracoscopy

3.3 Specimen collection and transport for microbiological investigations

Table 4: Specimen collection and transport for microbiological investigations

Special notes	Container	Volume	Storage & transport
• **Pleural Fluid:**			
Pleural effusion /fluid is a suboptimal specimen as tubercle bacilli are mainly in the pleura. **A pleural biopsy specimen is preferable to pleural fluid.**	For culture – Sterile, screw capped, transparent container	20-50ml of pleural fluid	should be transported in three-layer packaging at 02-08°C in cool boxes
• **Biopsies and tissues**			
Should be taken under sterile conditions and be placed in sterile containers without fixatives or preservatives. For prolonged transportation, dehydration should be prevented by adding sterile saline (01 ml 0.9% saline) to keep the moisture.	Sterile, screw capped, transparent container for TB culture and molecular tests		should be transported in three-layer packaging at 02-08°C in cool boxes
• **Body fluids -** • **(cerebrospinal fluid, pericardial fluid, synovial fluid, peritoneal fluid)** • **Fine-Needle Aspirates (FNA)** • **Pus**			
Should be taken under sterile conditions using aspiration techniques or surgical procedures and be placed in sterile containers **without** fixatives or preservatives (Formal saline/Formalin)	Sterile, screw capped, transparent container for TB culture and molecular tests	2-5 ml	should be transported in three-layer packaging at 02-08°C in cool boxes
• **Bone marrow**			
Should be taken under sterile conditions using aspiration techniques and be placed in sterile containers **without** fixatives or preservatives (Formal saline/Formalin) **GeneXpert is not performed.**	For culture – Sterile, screw capped, transparent container.	2-5ml of Bone marrow aspirates	should be transported in three-layer packaging at 02-08°C in cool boxes

• **Urine**			
Urine is expected to be contaminated. To minimize excessive contamination of urine specimens, external genitalia should be washed before specimen collection. As excretion of tubercle bacilli is intermittent, three consecutive early-morning midstream specimens must be collected.	Sterile, screw capped transparent container for TB culture	20-50ml	should be transported in three-layer packaging at 02-08°C in cool boxes

Figure 2: Containers for sputum smear and culture & molecular tests

Clean, transparent screw capped container for sputum smear microscopy

Sterile, screw capped, transparent container for TB culture and molecular tests

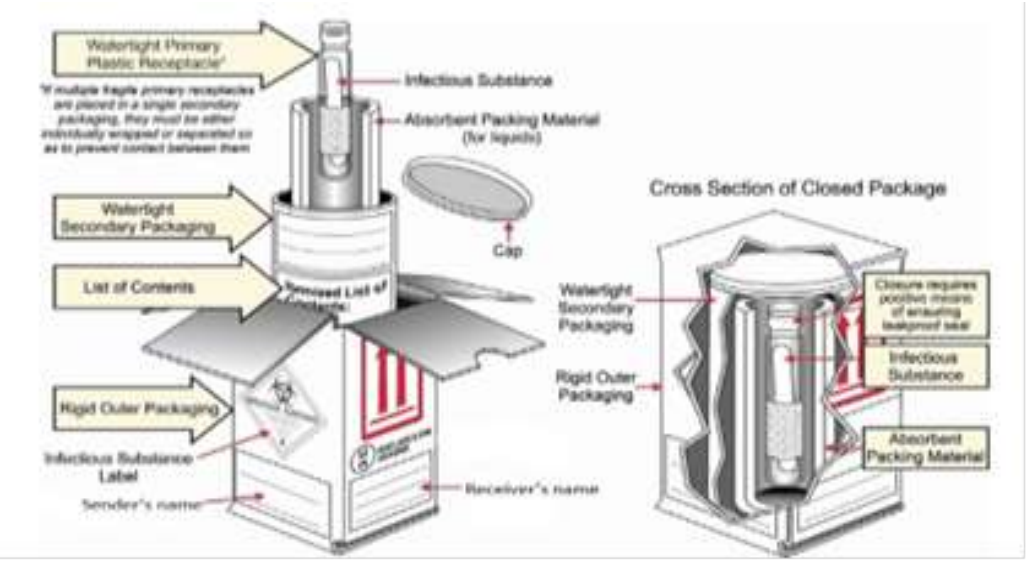
3.3.1 Storage of specimens

The recovery of MTBC decreases with time and this is especially critical for EPTB specimens due to paucibacillary nature. If specimens cannot be transported to the laboratory within one hour, it is recommended to store them at 02-08°C.

3.3.2 Transport of Samples (Smear, Xpert MTB/RIF Ultra, Culture)

Just as collection, transporting in appropriate conditions and submitting the specimen to the laboratory as quick as possible are of equal importance. Every effort must be made to organize and expedite specimen transportation and processing. Specimens, including clinical specimens and culture isolates should be transported from one laboratory to the other in three- layer packaging at 02-08°C in cool boxes as mentioned below.

Figure 3: Diagrammatic representation of three- layer packaging



Primary receptacle: A watertight, leak-proof receptacle containing the properly labelled specimen. The receptacle should be wrapped in adequate absorbent material to absorb all fluid in case of breakage.

Secondary receptacle: A durable, watertight, leak-proof receptacle to enclose and protect the primary receptacle. Sufficient absorbent material must be used to cushion multiple primary receptacles if few primary receptacles are placed in one secondary receptacle. E.g., A disposable zip lock polythene/plastic bag/plastic container.

Third receptacle (Outer package): The outer most package which protects the package from physical damage and water. The secondary receptacle is placed inside this receptacle. Request forms should not be kept inside the 3rd receptacle (cool box).

When transporting specimens (e.g., TB culture isolates) outside the country, the regulations specified by the International Air Transport Association (IATA) for international transfer of infectious substances, should be followed. The laboratories receiving specimens should check and document the temperature at the receiving counter itself.

Personal Protective Equipment (PPE) is not necessary for people who transport specimens in the triple package.

3.4 Supportive investigations

3.4.1 Biochemical investigation

Bio chemical makers such as adenosine deaminase, gamma interferon are dealt in detail under relevant sections.

3.4.1.1 Baseline investigations

- ESR
- CRP
- HIV
- FBC
- FBS
- Liver profile
- Renal profile

The above investigations may be carried out as indicated.

3.4.1.2 Interferon-Gamma Release Assays (IGRA)

IGRA are new, in vitro T-cell based assays that measure interferon-gamma (IFN-γ) production. They operate on the basis that T-cells previously sensitized to TB antigens produce high levels of IFN-γ when re-exposed to the same mycobacterial antigens. Two tests in commercial use are the QuantiFERON TB Gold Plus (QFT-Plus) and T-SPOT. Early IGRAs used PPD as the stimulating antigen, newer assays use *M. tuberculosis*-specific proteins – the early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP10) – encoded by genes located within the RD-1 segment of the *M. tuberculosis* genome. These antigens are not found in Bacillus Calmette Guérin (BCG) and many Non-Tuberculosis Mycobacteria (NTM) species. It requires only a single patient visit and the result will be available within 24 hours. In addition, it does not boost responses by subsequent tests and the result is not affected by previous BCG vaccination.

3.4.1.3 The TST

TST is a supportive tool to diagnose TB infection. It is more useful in diagnosing EPTB than PTB.

3.4.2 Radiological investigations

3.4.2.1 Chest x rays:

In EPTB, CXR is mandatory. This may provide a clue to co-existence of PTB or evidence of previous exposure.

3.4.2.2 Other radiological investigations

X ray of other affected sites may be useful in supporting diagnosis, mainly bone and joint TB. Depending on the site of involvement, other radiological investigations such as ultra sound scan (US), Echocardiography, CT, magnetic resonance imaging (MRI) and other specialized tools can be used as supportive investigations.

3.4.3 Pathology (Histology)

The entire or part of the tissue sample taken from the affected organ can be used for histological examination and needs to be sent in formal saline. It is mandatory that, tissue samples are sent for microbiological investigations such as smears and culture in 0.9% saline.

In EPTB Chest X-Ray is mandatory

In microbiology for EPTB, tissue samples must always be sent in 0.9% saline

3.4.4 Invasive investigations

For the purpose of sampling of affected tissue, several invasive investigations are used according to the site of involvement. They include aspiration and true cut biopsies, bronchoscopy, thoracoscopy, other endoscopic biopsies like colonoscopy, laparoscopy and major procedures like laparotomy.

3.5 References

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Chapter 4: BONE AND JOINT TUBERCULOSIS

TB has been a problem for humans since antiquity. There is archeological evidence that deformities of bones and joints from this disease occurred in the ancient world notably with spinal TB identified in Egyptian mummies dating back 9000 years.[1,2]

Skeletal TB refers to tuberculous involvement of the bones and/or joints and comprises a group of serious infectious diseases. It is identified as the third most frequent localization of EPTB accounting for 10 to 35 percent of cases.[3] The most common form of skeletal TB is Pott's disease, a disease of the spine. This entity comprisesapproximately half of skeletal TB cases. The next most common form of skeletal TB is tuberculous arthritis, followed by extraspinal tuberculous osteomyelitis.[4]

Skeletal TB is a paucibacillary disease. *Mycobacterium tuberculosis* is by far the most common cause of mycobacterial osteomyelitis and arthritis worldwide.[5] The incidence of skeletal TB has increased in the past two decades, especially in underdeveloped countries, in part due to the AIDS epidemic. The proportion of skeletal TB among individuals with HIV infection is comparable with the proportion of skeletal TB among individuals without HIV infection.[3]

NTM also rarely cause musculoskeletal TB. It's incidence toohas increased in the 1980s and 1990s in relation to the AIDS epidemic. NTM infections have been associated with a previous injury or puncture wound, and with orthopedic surgery, such as hip or knee arthroplasty.[6,7] Furthermore, in recent years, *M. bovis* skeletal infectionshave been reported after intravesical BCG therapy.[8]

4.1 Pathogenesis

Tuberculous osteomyelitis and arthritis generally arise from reactivation of bacilli lodged in bone during mycobacteremia of primary infection. In most cases, reactivation is prevented, and they are contained to small, infected foci by local adaptive immune processes, and the infection is subclinical. CD4 and CD8 lymphocytes play important roles, as does IFN-γ.[9]

However active TB disease can develop immediately or after decades of latent infection. In highly endemic regions, musculoskeletal TB usually manifests clinically in the year following primary lung infection and therefore, occurs more frequently in relatively young patients.[10] Outside highly endemic areas, musculoskeletal TB is more commonly associated with late reactivation of infection and occurs mainly in adults. The likelihood of reactivation of infection

with progression to clinically apparent disease increases when local immune defenses fail, as inthe settings of malnutrition, advancing age, HIV infection, or advanced kidney disease.[11]

4.2 Types of skeletal TB

- Spinal TB osteomyelitis
- Peripheral TB osteomyelitis
- Peripheral TB osteoarthritis
- Multifocal osteoarticular TB
- Osteoarticular TB in special situations
- Skeletal TB due to NTM
- *Mycobacterium bovis* (BCG) osteoarticular infections

4.3 Diagnosis

1. Plane radiography - In the early stages, the tuberculous changes in joints are absent or non-specific. Soft tissue swelling with little periosteal reaction, osteopenia, narrowing ofthe joint space and subchondral erosions of both sides of the joint suggest TB. In some cases, Phemister triad may be observed – (juxta-articular osteopenia/osteoporosis, peripherally located osseous erosions, and gradual narrowing of the joint space)

2. MRI - This is the preferred imaging technique for spinal TB because it can demonstrate extension of the diseases into the surrounding soft tissues, differentiate from other possibilities, and assess the degree of bone destruction and compression effects on nerve tissues. The pattern of bone destruction in TB shows a low signal on T1-weighted imagesand a bright signal on T2-weighted images in affected vertebral bodies and the intervertebral discs are relatively preserved. The heterogeneous enhancement may differentiate spondylitic TBfrom pyogenic spondylitis, where the disc is usually markedly affected and shows peridiscal bone destruction and homogeneous enhancement.

3. Hematological data alone contribute little to the diagnosis, and the leukocyte count isusually normal. The erythrocyte sedimentation rate (ESR) and C-reactive protein concentration are often raised, but levels are lower than those seen in pyogenic vertebral infections.

4. CT scan - Bone anatomy and abnormalities, including calcifications and sequestra, arebetter seen.

5. Mantoux skin test is beneficial in the diagnosis of skeletal disease, particularly in communities where the incidence of TB is high. It can be helpful in confirming a diagnosis of TB, but a negative result cannot exclude it.

6. Chest radiographs - Evidence of pulmonary disease is found only in less than 50% of patients with osteoarticular TB, but active pulmonary disease is present in less than 1 in 5.[12] However, a chest radiograph is a must since it may help in decisions regardingpatient isolation and infection control.

7. Fine needle aspiration biopsy - May be performed under ultrasound or Computed Tomography (CT) guidance. Granulomatous reaction, with or without caseation necrosis, was found in 73%, Acid- fast bacilli were found in 64%, and the MTB cultures were positive in 83% ofall cases.[13] A positive Ziehl-Neelsen staining for acid-fast bacilli do not differentiate between tuberculous and non-tuberculous mycobacteria (NTM).

8. DNA detection by PCR may increase sensitivity of mycobacterial detection and allow for exclusion of NTB.

9. Operative specimens from joints and bones

- Purulent material or synovial fluid may reveal positive mycobacteria on direct smear(in 27%), and on culture (in 63%).[14]

- Synovial fluid findings are usually nonspecific; the white cell count can be high orlow, with preponderance of either neutrophils or lymphocytes.

- Synovial biopsy may be required to grow the organism.

- Sinus-track specimens are an excellent source for isolation of mycobacteria.

- Histological investigations on bony lesions, synovium or soft tissue masses areimportant.

- Molecular diagnostic techniques like the PCR and other forms of nucleic amplification tests are being applied to tissue samples. Although DNA-based PCR can be quite sensitive, it may not distinguish between viable and non-viable bacilli. The available data suggest that Xpert and the more sensitive Xpert Ultra may be useful adjuncts to diagnosis of skeletal TB, with sensitivity of 79% and 91%, respectively.

Rarely, mycobacterial, and pyogenic bacterial infections may be found concomitantly from operative specimens of spinal TB. Therefore, an initial isolation of pyogenic bacteria from operative or sinus specimen does not exclude the possibility of TB.

4.4 Treatment

The goals of treatment of osteo-articular TB are to contain and eradicate the infection, relieve pain, and preserve and restore bone and joint function. Most patients are expected to achieve healing with normal function if diagnosed and treated at an early stage. The main reason for poor outcome is the delays in diagnosis.

The cornerstone of treatment is combined anti-tubercular chemotherapy and active or assisted non-weight bearing exercises of the involved joints throughout the period of healing. An initial period of rest is to be followed by supervised gradual mobilization.

Anti-tubercular chemotherapy should not be delayed waiting for culture results because delays in treatment may result in less-than-optimal outcome. A four-drug ATT regimen should be used empirically until susceptibility information becomes available. INHand rifampin should be administered during the whole course of therapy. Additional drugs are administered during the first 2 months of therapy and generally are chosen from among the first-line drugs, such as pyrazinamide and ethambutol. In cases of drug resistance, the use of second-line medications is indicated.

The optimal duration of treatment is somewhat controversial. It should be individualized and based on the resolution of active symptoms and clinical stability of the patient.

In spinal TB, stabilizing the spine from the initial period of ATT which should be done in collaboration of orthopedics, neurosurgeons, and rheumatology teams. various types of spinal support in the form of collars, braces, and corsets, may beneeded. Adequate nutritional support is also essential, as in all forms of TB.

4.5 Surgery

Surgical intervention is warranted for patients in the following circumstances.

- Patients with spinal disease and advanced neurological deficits.
- Patients with spinal disease and worsening neurological deficits progress while on

appropriate therapy.

- Patients with spinal disease and kyphosis >40 degrees at the time of presentation
- Patients with chest wall cold abscess

Forms of surgical intervention may include decompression, use of hardware for stabilization of spine, abscess drainage, and/or debridement of infected material. In some circumstances, reconstructive surgery may be important once antimicrobial therapy has been completed.

4.6 Monitoring clinical response

The response to therapy may be monitored by clinical indicators such as pain, constitutional symptoms, mobility, and neurologic findings. Typically, these responses are relatively slow. Therole of inflammatory markers in monitoring the response to TB therapy is limited. It is not useful to perform serial radiographs since radiographic findings may appear to progress even during appropriate treatment.[10] Patients with mild weakness and lower paraplegia scores are more likely to recover completely by six months than patients with more severe prognostic indicators.[10]

For patients on antituberculosis therapy for skeletal TB in the setting of antiretroviral treatment (ART) for HIV infection, it is important to monitor for immune reconstruction inflammatory syndrome (IRIS). IRIS typically presents with paradoxical progression of TB clinical manifestations and constitutional symptoms in the first few weeks following initiation of ART.

4.7 Specific types of skeletal TB

4.7.1 Spinal TB osteomyelitis (Pott's disease)

Tuberculous spondylitis (TS) is the most common form of bone and joint TB. It affectsthe thoracic or thoracolumbar segment in around half of the cases, followed by the lumbar segment, and to a much lesser extent, the cervical segment. Multifocal non-contiguous spinal involvement is uncommon.

Progression of infection generally begins with inflammation of the anterior aspect of intervertebral joints and typically, it spreads behind the anterior ligament to involve the adjacent vertebral body. Once two adjacent vertebrae are involved, infection enters the

adjoining intervertebral disc space. This tends to occur later in Pott's disease than in bacterial vertebral osteomyelitis and may have the radiographic appearance of relative disc sparing.

Eventually, the avascular disc tissue dies and there is vertebral narrowing and subsequent vertebral collapse. Gibbus deformity, a form of structural kyphosis, can distort spinal canal anatomy. The spinal cord is then at risk of compression resulting in paraplegia, especially with involvement of the mid-thoracic region where the spinal canal is relatively "tight" around the cord. Occasionally, late-onset paraplegia occurs due to osteophytes and other chronic degenerative changes at the site of previous infection. Formation of a soft tissue mass, the "cold abscess" at the site is common.[10]

4.7.1.1 Clinical features

Tuberculous spinal infections should be suspected in patients presenting with insidious, and progressive back pain, especially when thoracic vertebrae are affected, witha pattern of bone destruction and relative disc preservation, and paravertebral or epidural soft tissue masses are observed.

The mean age of patients with this disease is 45–60 years. Back pain is the most prominent symptom (83–100 %), and only one-third of patients have fever or constitutional symptoms.

4.7.1.2 Complications

1. Neurological complications

Neurological complications, by far, are the most common complication of spinal TB. The frequency of thoracic spine involvement, the insidious course, and the resultant diagnostic delays explain the higher incidence. The neurological complications are in the forms of compression of the spinal cord, the cauda equina or other nerve roots. Patientswith thoracic or cervical spinal TB may have a risk of developing paraplegia or tetraplegia and are more common in patients with associated epidural abscesses.

During active disease, paraplegia can result from mechanical compression on the spinal cord by an abscess, granulation tissue, tubercular debris and caseous tissue, or by mechanical instability produced by pathological subluxation or dislocation. In rare cases, paraplegia is caused by edema of the spinal cord, myelomalacia, or direct involvement of the meninges and cord by tubercular infiltration (tuberculous spinal leptomeningitis), infective thrombosis, or

endarteritis of the spinal vessels. In patients with severe deformity, paraplegia can develop months or years after the lesion has healed due to stretching of the spinal cord over an internal anterior bony projection, producing gliosis.In this situation, MRI shows severe cord atrophy or syringohydromyelia, or constrictive scarring of and around the dura.

2. Spinal deformity

The development of kyphosis is the rule rather than the exception. It is caused by collapse in theanterior spine. Lesions in the thoracic spine are more likely to lead to kyphosis than those in the lumbar spine.

Vertebral collapse of a lesser magnitude is not considered an indication for surgery because, with appropriate treatment, it is less likely to progress to a severe deformity. Inchildren, kyphosis may continue to increase even after the lesion has healed.[15]

Progression of kyphosis can also occur after surgery and is worse when anterior resection and fusion alone are performed. It is less severe when surgery includes bothanterior and posterior fusion.

3. Other complications

3.1. Paraspinal masses - A cold abscess can occur if the infection extends to adjacentligaments and soft tissues. Abscesses in the lumbar region may descend under the sheath of the psoas (a psoas abscess) to the femoral trigone region and eventually erode into the skin.

3.2. A large retropharyngeal abscess - may be seen in exceptional cases of TB in thecervical spine presenting with hoarseness and problems with swallowing.

3.3. Tubercular pseudoaneurysm of the aorta - A rare complication of Pott's disease secondary to extension of an adjacent tubercular vertebral lesion to the aortic wallor due to tubercular arteritis.

4.7.1.3 Differential diagnosis Tuberculous spondylitis (TS)

- Primary or metastatic neoplastic disease, which usually affects the bone (vertebral body) and spares the intervertebral disc (except in primary vertebral myeloma, somecases of lymphoma, and rare cases of solid organ tumors such as thyroid neoplasms).
- Pyogenic spondylitis (PS)

- Brucellar spondylitis (BS) - in endemic areas

Molecular techniques such as multiplex real-time PCR may be useful for rapid diagnosis of TS against PS and can distinguish typical from atypical mycobacteria. These techniques may be useful in drug-resistant cases too. Nonetheless, these techniques are not indicative of disease activity because they cannot differentiate between living and dead microorganisms.

4.7.1.4 Treatment

The indications for surgery and type of surgery performed are case-specific decisions.

1.) Surgery, combined with prolonged specific antituberculosis chemotherapy are mainly indicated for neurological complications, spinal deformity, or instability. It is needed in more than 50 % of cases, especially in patients with a delayed diagnosis. Surgical correction of spinal deformity is easier to perform in active disease than in healed disease. This treatment provides satisfactory results in most cases. Surgical treatment isusually indicated even for minimal neurological deficits.

However, in some cases using only antituberculosis therapy and rest may yield equally good results. Thus, although surgery is usually mandatory, when the neurological deficitis secondary to mechanical compression due to a fluid collection in the extradural spaceand the spinal cord is relatively preserved (edema without myelomalacia), conservative treatment may be effective. Here, if the neurological deficit persists or worsens, surgical decompression should be performed.

2.) In spinal TB with no neurological deficits, conservative treatment with a combination of antituberculosis drugs yields similar long-term results. The indications for surgery and type of surgery performed are case-specific decisions.

4.7.2 Peripheral tuberculous osteoarthritis and osteomyelitis

These terms are used for extraspinal skeletal TB that affects joints and bones. Articular TB is a slowly progressive chronic disease that usually presents as mono-arthritis. Long weight-bearingbones are usually affected, and arthritis of weight-bearing joints, knee, hip, and ankle is relatively common. Femoral disease (including trochanteric tuberculous bursitis) is not rare.

The ribs, sacroiliac and sternoclavicular joints are sometimes affected. TB is one of the most common causes of rib osteomyelitis. TB can also affect the tendon sheaths and is one ofthe causes of tenosynovitis of the hand and carpal tunnel syndrome. The diagnosis is usually delayed because *M. tuberculosis* is an uncommon etiology of these conditions.

In tuberculous osteoarthritis tubercle bacilli are deposited in the synovium via a hematogenous route but may also gain access through direct penetration from a metaphyseal focus of osteomyelitis where a previous traumatic injury may be the precipitating event.

The earliest manifestation of articular TB is pain, which may precede signs of inflammation for weeks or months. Fever and systemic symptoms are usually absent. Peripheral tuberculous osteomyelitis usually presents as a cold abscess, with swelling and mild erythema and pain, andmay be misdiagnosed as a tumor.

The early stages are often misdiagnosed, and the joint disease is attributed to other causes. The diagnosis requires a high index of suspicion and is usually established through arthrocentesis and mycobacterial studies. However, synovial biopsy is often needed. Radiographs may initially show soft tissue swelling, but later osteopenia, periosteal thickening, and periarticular bone destruction are observed. Cold abscesses and fistulae develop in late cases. Chest radiographs show pulmonary disease in one-third to one-half of cases, but active pulmonary TB is infrequent.

Prolonged antituberculosis therapy results in complete resolution in early diagnosed cases. Surgery is necessary in advanced cases and may require arthrodesis or arthroplasty.

4.7.3 Special Osteoarticular Tuberculous Infections

4.7.3.1 Prosthetic joint infection

Prosthetic joint infection (PJI) due to *M. tuberculosis* is rare and the typical case is misdiagnosed. Patients who present with knee or hip osteoarthritis, are treated with joint arthroplasty, and later develop culture-negative chronic PJI, sometimes years after the procedure. The diagnosis is often difficult and should be suspected in culture negative PJI with histological features of granulomatous lesions with macrophages and multinucleate cells with or without caseum. The diagnosis is confirmed by isolation of the microorganism on TB culture or by molecular techniques (PCR). In some cases, administration of immunosuppressive

therapy is the precipitating event, including administration of anti-tumor necrosis factor (infliximab).

Resection arthroplasty or arthrodesis has been used to treat this type of PJI, but whenthere is no loosening of the prosthesis, the patient may cure with debridement, exchange of plastic components while retaining the prosthesis, and prolonged antituberculosis therapy (9–12 months).

4.7.3.2 Sternal TB

TB of the sternum is rarely reported and accounts for 1.5 % of bone and joint TB cases and may follow coronary artery bypass surgery, a presentation of underlying mediastinal TB, or as primary sternal osteomyelitis. Primary sternal TB is relatively more common than TB secondary to CABG and the diagnosis should be suspected in recurrent culture-negative nonhealing sternal wounds and confirmed by histology and specific culture. Surgery is justified in refractory cases of ATT, whenever there is a doubt about the diagnosis, to remove a large sequestrum, or when there arelarge abscesses.

4.7.3.3 Tuberculous sacroiliitis

The sacroiliac joint is affected in 4–9.5 % of patients with musculoskeletal TB. Misdiagnosis is common and attributed to the inaccessibility of the sacroiliac joint. Tuberculous sacroiliitis should be differentiated from pyogenic sacroiliac bone infections (usually acute), and from chronic diseases (e.g., osteoarthritis), inflammatory diseases (e.g., rheumatoid arthritis), ankylosing spondylitis and Reiter's disease, gout and pseudogout, tumor-like conditions (e.g., pigmented villonodular synovitis), and in endemic areas, from brucellar sacroiliitis. Currently, anti-tuberculostherapy is the treatment of choice. Surgery (arthrodesis) is used in patients with large periarticular abscesses and those with persistent pain.

4.7.3.4 Tuberculous trochanteric bursitis

Primary TB of the trochanteric area, a relatively common manifestation of the diseasein the pre-antituberculosis drug era, is now a rare condition accounting for less than 2 % of musculoskeletal TB cases. The pathogenesis of tuberculous trochanteric bursitis (TTB) has not been well defined, and it is uncertain whether the bone or the bursa is first affected by hematogenous infection. Recent trauma, immunosuppression, or local corticosteroid infiltrations may contribute to the spreadof the disease.

Mild pain, swelling, and stiffness in the lateral aspect of the thigh with no functional limitations are often present for months before the diagnosis is established. Fever orgeneral symptoms are usually absent. This dearth of symptoms, together with a low clinical suspicion, accounts for the usual diagnostic delay. The diagnosis is commonlymade in advanced phases, when a cold abscess or draining fistula that does not respond to conventional antibiotic therapy alerts the clinician.

TTB has a marked tendency to relapse, and ATT alone has beensuccessful only in a few cases if started at the early stage of the disease. Surgery should be considered for most patients. Thorough excision of the bursa and all necrotic tissue and fistulous tracks is mandatory for cure but, extensive trochantericexcision has higher resolution rates than bone curettage. Patients are usually treated for 12 months with ATT.

4.7.3.5 Multifocal osteoarticular TB

Multifocal bone TB is considered rare, accounting for 7–11 % of osteoarticular TB cases. In these ≥ 2 noncontiguous vertebra or 4-6 bones or joints are affected. Whole-body scintigraphy may be useful to detect occult lesions. The duration of ATT in these extensive bone infections is unknown, but most patients are treated for longer than 24 months.In children, flat bones of hands and feet are commonly involved.

4.7.4 Nontuberculous mycobacterial infections (NTM)

Approximately 60 of the more than 125 nontuberculous mycobacterial species can cause disease in humans.[15] The prevalence of NTM infections in humans is unknown. *M. avium-intracellulare* (MAI) is the most isolated NTM species, mainly in patients with HIV infection/AIDS; *M. fortuitum* and *M. kansasii* are also relatively frequent.

NTM soft tissue infections are common, but skeletal disease is rare. Soft tissue infections are usually the result of direct inoculation occurring during penetrating trauma, open surgery (such as mediastinitis and sternal wound infections after cardiothoracic surgery), after injection of steroids or local anesthetics. Rapidly growing mycobacteria (e.g., *M. abscessus, M. chelonae, M.fortuitum*) are the most isolated agents. The clinical course is usually indolent, with painful red to violaceous nodules that can drain serosanguineous material, ulcerate, or spread to deeper tissues and form fistulous tracts.

Skeletal infections due to NTM are rare and have been observed in cluster outbreaks in cardiothoracic surgery (sternal osteomyelitis due to *M. fortuitum or M. abscessus)* or in isolated cases of *M. xenopi* arthritis after joint arthroplasty.

Histological studies show abundant neutrophils and caseum, although non-caseating granulomas may also be observed. The acid-fast bacilli test is usually negative. Previously, identification of NTM species was a tedious process involving biochemical tests that required weeks of culturing. Nowadays, the relevant species are identified by molecular techniques.

When managing osteoarticular infections due to NTM, surgical excision of the infected tissue and/or prosthetic joint removal should be performed. A minimum of 18 months of specific antimycobacterial chemotherapy is recommended, and the regimen can be extended to 12 or more months in patients with disseminated disease.

4.7.5 *Mycobacterium bovis* (BCG) osteoarticular infections

Intravesical instillation of bacillus Calmette Guérin (BCG), which is used to treat superficial bladder carcinoma, can rarely be associated with arthritis/arthralgias (0.5 %). *M. bovis* BCG intravesical instillations have been anecdotally associated with skeletal infections, particularly spondylitis, which may present as late as 12 years after the procedure, and with hip or knee arthroplasty. The diagnosis is established by culture and recently, by PCR-based genomic analysis. Because *M. bovis* is resistant to pyrazinamide, the usual antimycobacterial regimen consists of INH, rifampin, and ethambutol administration for as long as 12 months.

4.7.6 Inflammatory (Poncet's disease) - Tubercular rheumatism

Poncet disease is an acute symmetric polyarthritis involving large and small joints associated with active extrapulmonary, pulmonary, or miliary TB. In general, there is inflammation of theinvolved joints but no objective evidence of active TB. Poncet's disease is relatively rare, and the pathogenesis is unclear, and it is probably immune mediated. HIV coinfection is also a riskfactor. The arthritis generally resolves within a few weeks of initiation of anti-TB therapy, withno residual joint destruction.

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Chapter 5: TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM

5.1 Introduction

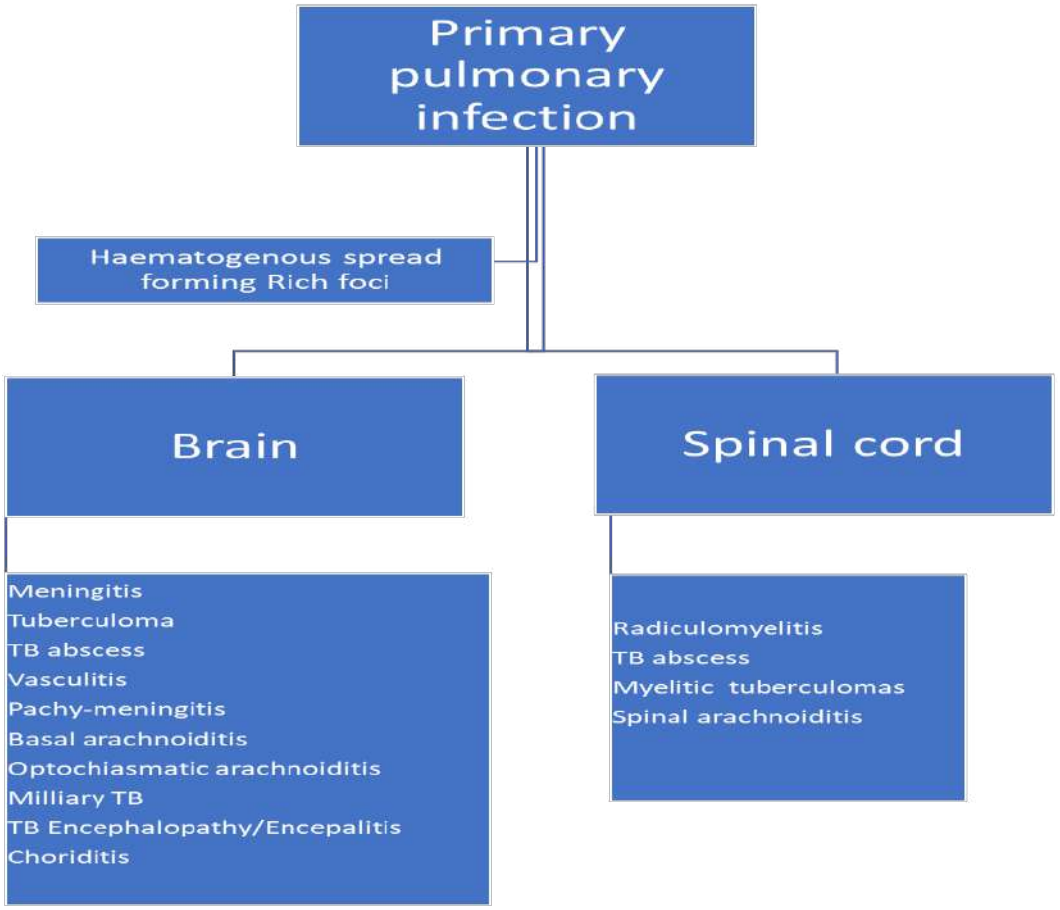
- Central Nervous System Tuberculosis (CNS TB) is a medical emergency that carries a high mortality rate especially when the diagnosis is delayed. Despite treatment, a significant proportion of patients end up with permanent neurological sequalae. Therefore, early diagnosis and proper treatment are crucial to improve outcomes.
- CNS TB can be mimicked by several other conditions such as sarcoidosis, melioidosis, lymphoma, cerebral metastasis, demyelinating disorders, and fungal infections. Therefore, it is important to rule out these conditions.
- Definitive diagnosis of CNS TB with microbiological or histological confirmation is possible only in a small percentage of patients. Therefore, on clinical and other grounds, ATT has to be commenced in a large proportion of patients. It is important to carefully monitor these patients while they are being treated with ATT.
- All patients suspected of CNS TB should be screened for concurrent tuberculous involvement of the lungs and other extrapulmonary sites.
- Treatment regime of CNS TB differs from the regime used in pulmonary TB with a longer course of ATT.
- Close follow-up of patients treated for CNB TB is important to identify
    - poor responders to treatment
    - treatment related immunological reactions early
    - complications of disease and treatment
    - other conditions that may mimic TB

5.2 Pathogenesis

- CNS TB results from haematogenous spread of *M. tuberculosis* from a primary pulmonary infection leading to formation of small subpial and subependymal foci (rich focus) in the brain or spinal cord. Rarely CNS TB can spread from contiguous adjacent structures.
- In TB meningitis, these bacilli proliferating in rich foci can rupture into the subarachnoid space resulting in the clinical manifestation of meningitis. Some of these foci will enlarge in their original site leading to the formation of tuberculomas.
- *M. tuberculosis* is known to exploit the host cytokine signaling for proliferation and invasion.

- Occasionally, the host immune response can become overactive, leading to what is known as cytokine storms. This excessive immune response due to the cytokine storm can lead to further damage to the central nervous system.
- Patients with more severe disease tend to have higher level of inflammatory cytokines, especially Interleukin-6 (IL-6). In addition, other inflammatory cytokines such as IFNγ, TNFα, IL-17A, and IL-1β can also be elevated.

Figure 4: Pathogenesis of CNS Tuberculosis



5.3 Clinical features of CNS TB

Clinical features of the CNS TB depend on the anatomical location of the Central Nervous System(CNS) infection and the severity of the infection.

Depending on the location, CNS TB can present as meningitis, tuberculomas, spinal TB and other uncommon presentations (Figure 4).

Symptoms of CNS TB are variable. Headache, vomiting, altered sensorium, and systemic symptoms such as fever, loss of appetite, weight loss, and night sweats are some of the common

symptoms. In addition, they can also develop seizures and focal neurological deficits. Often these symptoms tend to develop in a subacute manner.

5.3.1 TB meningitis

TB meningitis can be broadly staged into 3 phases according to the progression and clinical features (Figure 5).

Figure 5: The three phases of TB meningitis

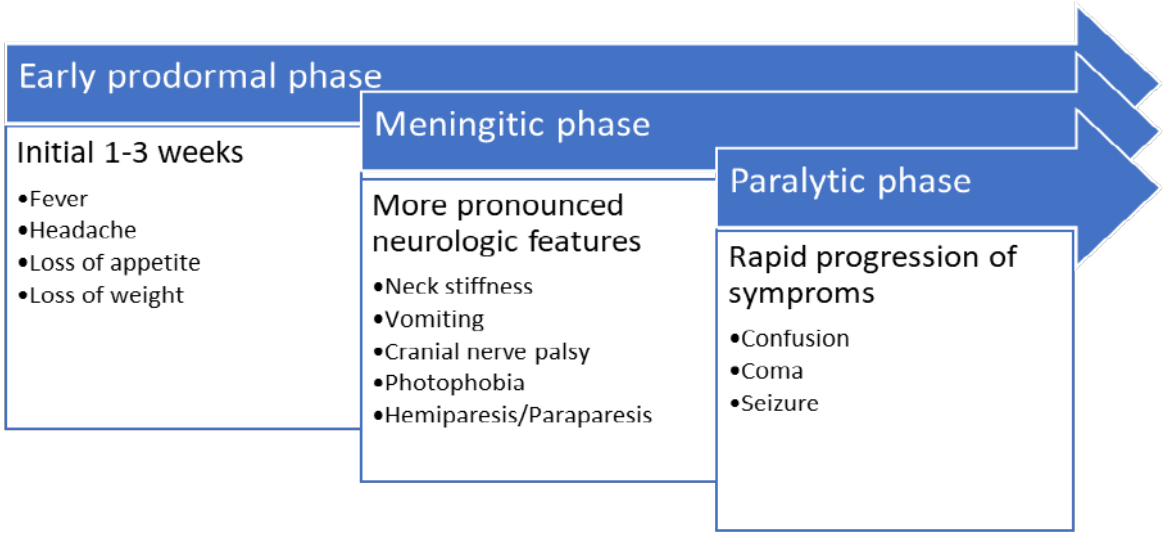


Table 5: Modified British Medical Research Council criteria for grading the severity of TBM

Grade	Criteria
1	Glasgow Coma Scale (GCS)15, no focal neurology
2	GCS 11-14 or GCS 15 with focal neurological deficits
3	GCS ≤ 10

In addition, the modified criteria of British Medical Research Council have defined three grades of tuberculous meningitis (TBM) depending on the severity (Table 5). Progression from one stage to the other worsens the prognosis. The level of consciousness at the time of hospital admission and the time to initiation of ATT are two important prognostic factors in TBM.

5.3.2 Tuberculomas and abscesses

- These can occur in the brain or in the spinal cord.
- The clinical presentation will depend on the anatomical location and the size of the lesions. Patients with cerebral lesions can develop focal neurological signs, seizures, headache and alteration of the sensorium or personality.
- Tuberculomas and abscesses can coexist with TBM.

5.3.3 TB Myelitis

The clinical features of TB myelitis depend on the level of the spinal cord involved and the extent of myelitis. Patients can present with paraparesis or quadriparesis with or without bladder and bowel involvement.

5.4 Investigating CNS TB

5.4.1 CSF analysis in CNS TB

Once an adequate Cerebro Spinal Fluid (CSF) volume is obtained, it is important to transport the samples as quickly as possible to the laboratory as any delay in analysis can lead to disintegration of the lymphocytes. A 10-15 ml (at least 6 ml) of CSF volume has to be sent for analysis. CSF volume more than >5 ml received at the laboratory enables concentration of the specimen by centrifugation and use the deposit for better yield.

The blood glucose accompanying the CSF should be tested ideally one hour before the lumbar puncture and both blood and CSF samples to be sent promptly.

In patients with poorly controlled diabetes with random blood glucose levels greater than 120 mg/dl, the CSF glucose interpretation can be unreliable due to the fluctuating glucose levels in the blood and the CSF.

Typical CSF analysis findings in TBM:

- CSF white blood cell count usually ranges between 50-500 cells/mm^3 with predominance of lymphocytes.
- CSF protein is frequently elevated.
- CSF glucose level drop of more than 40% compared to the plasma glucose.

Atypical CSF findings in CNS TB:

- Atypical CSF findings can be seen particularly in the immunosuppressed patients.

- Rarely CSF can be acellular or contain a predominance of neutrophils.
- When cerebrospinal protein content is very high (>1g/dL) a spinal block should be suspected.

For CSF smear, culture, and nucleic acid amplification techniques, please refer the microbiology section.

Table 6: CSF investigations with their usefulness in diagnosing CNS TB

Test	Confirms CNS TB	Strengths	Limitations	Sensitivity for diagnosis of TBM
Ziehl-Neelsen smear microscopy	Yes	Widely available.	Operator/ lab technician dependent.	~ 10–50% (will depend on the volume of CSF and the technique)
Xpert MTB/RIF	Yes	Rapid results. Rifampicin susceptibility status.	Cannot exclude TBM when negative.	~ 20–60%
Xpert MTB/RIF Ultra	Yes	Higher sensitivity than Xpert MTB/RIF. Rifampicin susceptibility status.	Cannot exclude TBM when negative. Not widely available in Sri Lanka.	~44–77%

- It is important to send CSF for Xpert MTB/RIF ultra or Xpert MTB/RIF in all suspected patients, as this has the highest yield with early availability of results.
- CSF for TB culture also has to be ideally sent in all suspected patients.
- Currently there is insufficient evidence to recommend routine testing for CSF Adenosine deaminase (ADA) and Chloride levels.

5.4.2 Histological Diagnosis

- In patients suspected of CNS TB, if routine non-invasive tests do not establish the diagnosis, biopsy to check histology is an option if there are lesions like tuberculomas which are amenable to biopsy.
- When biopsy is considered, it is important to pre-plan the sampling. This includes deciding on the ideal site/sites for the biopsy, and the other tests that can be done on the

sample taken (e.g., smear, culture and Xpert MTB/RIF Ultra). Ideally the treating physician, radiologist and the surgical, microbiology, and histopathology teams should be involved in the decision making.

5.4.3 Radiological investigations

5.4.3.1 Chest Xray

- A Chest Xray (CXR) should be done in all CNS TB patients.
- Significant proportion of patients with CNS TB have CXR evidence of active or healed PTB which will help support the diagnosis.

5.4.3.2 Cerebral Imaging

- Early brain imaging may provide clues to the diagnosis and will also provide important baseline information.
- Ideally, all patients evaluated for possible cerebral TB need to undergo a contrast enhanced CT or contrast enhanced MRI brain, as early as possible.
  - In TB meningitis there may be leptomeningeal enhancement.
  - In those with tuberculomas, the tuberculomas may be evident.
  - In addition, there may be evidence of complications such as hydrocephalus or infarcts.
- In cerebral imaging, tuberculomas appear as space-occupying lesions. Toxoplasmosis, sarcoidosis, metastases, CNS demyelinating conditions, neurocysticercosis, granulomatous conditions like IgG_4 related disease and lymphoma are radiological mimics of tuberculomas.

5.4.3.3 Imaging in TB myelitis

- TB myelo-radiculitis usually involves more than one spinal region, with the thoracic and cervical region being most affected.
- The MRI imaging of the spinal cord with contrast is superior to CT scanning and should be the preferred imaging modality in patients suspected of spinal cord involvement. MRI may show meningeal and radicular enhancement, myelitis/longitudinal extensive transverse myelitis (LETM) or intramedullary spinal tuberculomas.

5.5 Treatment of CNS TB

- ATT has a wide bacteriological coverage. Therefore, other bacterial infections also may partially respond to ATT. This must be kept in mind when CNS TB is treated.

- Concomitant use of steroids with ATT may improve other immune mediated CNS inflammatory conditions.
- Every measure has to be taken to confirm CNS TB, bacteriologically or histologically.
- When the clinical diagnosis of CNS TB is not confirmed bacteriologically or histologically, it is important to clearly document the grounds on which the probable diagnosis of CNS TB was made before starting ATT.

For further details, refer the general treatment section.

5.5.1 Anti Tuberculous Treatment in CNS TB

- Of the available antituberculosis medications, INH and pyrazinamide have the best Cerebro Spinal Fluid (CSF) penetration.
- Rifampicin is also very important to achieve successful treatment outcomes.

INH

- CSF/serum concentration ratio is approximately 40% with normal meninges.
- CSF levels rise and equals the serum level when the meninges are inflamed.
- Has potent bactericidal activity.
- Dose is 5-10 mg/kg/day orally for adults.
- All patient treated with INH should be given oral pyridoxine to prevent INH induced peripheral neuropathy.

Rifampicin

- CSF/serum concentration ratio is poor with normal meninges and rises to ~20% when meninges are inflamed (however it may still not reach the minimal inhibitory concentration even for pan-sensitive *M. tuberculosis*).
- Mortality rises when there is resistance to rifampicin highlighting the crucial role played by rifampicin in the treatment of CNS disease.
- Dose is 10-15 mg/kg/d orally for adults with a maximum dose of 600mg/day.
- Since the standard fixed dose ATT has only a daily dose of 450mg of rifampicin, there is a belief among certain clinicians that this dose is inadequate, and they recommend individual drugs with doses calculated according to the body weight to prevent underdosing of rifampicin. This may be mainly applicable to patients who are overweight. However, the maximum daily dose of rifampicin is 600mg.

Ethambutol

- CSF/serum concentration ratio is poor without meningeal inflammation but reaches adequate minimal inhibitory concentration levels in the presence of meningeal inflammation.
- Dose is typically 15 mg/kg/day orally; higher dose 25 - 35 mg/kg/day orally achieves better minimal inhibitory concentration but also increases the likelihood of optic neuritis.

Pyrazinamide

- CSF/serum concentration ratio is similar to INH.
- Dose is 25-35 mg/kg/day orally with a maximum daily dose of 2000 mg.
- It is well absorbed orally and achieves high concentrations in the CSF.

5.5.2 Steroids in CNS TB

It is recommended that all patients with TBM receive adjunctive corticosteroids regardless of disease severity at presentation.

- Corticosteroids reduce mortality but not morbidity.
- As the steroid, dexamethasone or prednisolone can be used as tapering dose over 6-8 weeks.
- Dexamethasone can be administered intravenously or orally;
  - first two weeks 0.4 mg/kg/day in three divided doses
  - third week 0.3mg/kg in three divided doses
  - fourth week 0.2mg/kg in three divided doses
  - fifth week, this is followed by 4mg daily for one week and then reduced by 1mg/kg weekly.
- Equivalent doses of prednisolone can be given as an alternative.

5.5.3 Aspirin in CNS TB

Aspirin should be considered for patients suspected of CNS vasculitis or cerebral infarctions secondary to TB.

5.5.4 Duration of treatment

- Treatment of TBM involves an initial intensive phase of 2 months (INH, rifampicin, pyrazinamide and ethambutol) followed by a continuation phase for 10 months (INH and rifampicin).
- If there is a clinical deterioration or worsening CSF biochemical parameters or worsening radiological features, the intensive phase can be extended. However, this should be a collective decision by the team of physicians involved.
- In the treatment of tuberculomas total treatment duration is 12 - 18 months. If there are concerns regarding adequacy of treatment due to new or enlarging lesions a longer period of treatment should be considered.
- In addition, the dose of rifampicin or pyrazinamide may be increased if new tuberculomas are emerging or size of tuberculomas are increasing while on standard ATT dosing.
- However, it is important to note that sometimes there may not be complete resolution of all tuberculomas radiologically at the point of completion of the treatment course.

5.6 CNS paradoxical reactions

Paradoxical reaction (PR) poses a challenge in the treatment of CNS TB since it is a diagnosis of exclusion. This can be misdiagnosed as treatment failure, drug resistance, tuberculous relapse, superimposed infection, or alternative diagnosis. Occurrence of PR is associated with female gender, concurrent HIV infection, shorter duration of illness and lower base line lymphocyte counts.

When treating PRs, steroids play a major role. Other immune modulatory agents like thalidomide or infliximab are also used in some instances.

As there are no trials to guide treatment, it is important to have a multi-disciplinary input in making treatment decisions of patients with complex PRs. For further details refer the section on PR.

Therefore, treatment of CNS TB needs to be individualized. This includes extending the intensive phase or the continuation phase and offering higher doses of rifampicin and pyrazinamide in certain patients with suboptimal response to the standard regime. These decisions are best made at a multidisciplinary team.

5.7 Bridging therapy

There may be situations where due to side effects, a bridging regime may need to be adopted. E.g., when liver functions become deranged with ATT.

Levofloxacin, ethionamide and linezolid are some drugs that have shown good CSF penetration that can be used in such situations for bridging. The regime for bridging should be decided in liaison with a chest physician.

In treating CNS TB patients with deranged liver function tests the threshold for switching to a bridging regime is higher (hepatic transaminase levels more than 5 times the upper limit of normal while in other situations it is 3 times the upper limit of normal). The hepatic transaminase levels should be monitored once in two days in these patients.

5.8 Complication in CNS TB

5.8.1 Hydrocephalus

- Hydrocephalus due to CNS TB can be either communicating or non-communicating. Communicating hydrocephalus is the more commonly seen presentation. Neuroimaging will help differentiate the two.
- Early shunting may need to be considered in patients with non-communicating hydrocephalus if there is progressive clinical deterioration due to hydrocephalus.
- Communicating hydrocephalus may be treated medically with frusemide, acetazolamide or repeated lumbar puncture.

5.8.2 Increased intracranial pressure

- Intracranial pressure can rise in CNS TB patients due to hydrocephalus, diffuse oedema due to TB encephalitis, tuberculomas and cerebral infarctions following vasculitis.
- Urgent surgical interventions may be indicated in some patients.
- Hyperosmolar therapy (IV Mannitol and hypertonic saline) and steroids can be used to treat raised Intra Cranial Pressure (ICP).

5.8.3 Hyponatremia

- Hyponatremia is a common complication of CNS TB.
- Hyponatremia in this setting could be either due to the syndrome of inappropriate anti-diuretic hormone (SIADH) or cerebral salt wasting syndrome.

- However, other causes of hyponatremia also should be carefully excluded.

5.8.4 Seizures

- Seizure can occur in CNS TB due to various reasons, Hyponatremia, vasculitis, tuberculomas, infarcts being some of the causes.
- When seizures occur, antiepileptic medication needs to be administered. When selecting antiepileptics, drugs which do not interfere with ATT should be considered.

5.8.5 Stroke

- Stroke can occur as a complication of vasospasm, thrombosis or vasculitis/vasculopathy.
- Most of the infarctions involves head of the caudate nucleus, anteromedial thalami and anterior limb and the genu of internal capsule.
- For those with intracranial vasculopathy, aspirin along with steroids should be considered.

5.8.6 Cerebral venous sinus thrombosis

Venous sinus thrombosis is another rare complication that can occur secondary to ongoing inflammation.

5.9 Follow-up of patients

- It is important to manage the comorbidities like diabetes and optimize the nutritional status while the patient is on ATT.
- Clinical response, CSF response, radiological response and drug side effects need to be closely monitored during the follow-up.
- Timing of repeat CSF analysis and radiological evaluations need to be decided according to the patient's clinical response and available resources.
- It's very important to clearly document the initial clinical grounds on which the diagnosis of CNS TB was made.
- Timeline of events indicating dates and results of initial CSF tests, microbiological tests and radiological studies and the date of initiation of ATT and steroids are important in patient follow up. Thus, it important to clearly document the above information.

It is imperative to continuously question the accuracy of diagnosis and to exclude mimics. It is worth establishing microbiological/histological diagnosis when there is a poor response or clinical deterioration while on treatment. Possibilities in such an instance include:

- Wrong diagnosis
- Inadequate dosing
- Drug resistance
- PR

5.10 CSF response in CNS TB patients following the commencement of ATT

Although CSF normalizes over time, the change of lymphocyte count and protein concentration is a slow process, limiting their clinical use in this aspect.

- The median time for CSF protein to normalization is 8 months.
- For CSF cell count, although the count usually drops by 50% after 1 month in 96% of patients, 36% of patients have abnormal CSF cell counts at 6 months and 16% of patients have abnormal CSF at 24 months.
- CSF glucose normalizes faster than CSF protein, with nearly half of the patients CSF glucose levels returning to normal after 1 month of commencing ATT and the majority normalizing CSF glucose at 2 months.
- CSF TB culture is usually sterile by one month of commencing ATT.
- In a clinical setting of a patient with a presumptive diagnosis of TBM who is deteriorating despite treatment, a repeat LP may be of value as the neutrophils and glucose should be changing in a rapid and predictable fashion. If these two parameters show no definite improvement on repeat LP, it should be considered atypical for TBM, and an alternative diagnosis or drug resistance should be considered.
- The differential rate of change between the lymphocyte and PMN cells, together with the rapid change in the glucose, is the most useful guide as the response to therapy.
- Since TB Xpert MTB/RIF Ultra can remain positive for months, if the initial TB Gene Xpert report is positive repeated TB Gene Xpert is not indicated unless you have diagnostic dilemma or suspect drug resistance.

5.11 Follow-up imaging and CSF studies in CNS TB patients

- Repeat CSF studies or radiological studies can be considered if clinically indicated.
- Follow-up CNS imaging should be considered if the patient has clinical deterioration despite good compliance with ATT. Contrast MRI or CT should be considered to look for complications such as hydrocephalus, infarcts, tuberculomas and PRs.

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Chapter 6: GENITOURINARY TUBERCULOSIS

6.1 Introduction

The term Genito Urinary Tuberculosis (GUTB) encompasses TB of the male and female genital tract and the urinary tract. The reported cases of GUTB account for 20-70% of EPTB. In developing countries, it is the 2nd most common extrapulmonary TB after the lymph nodes and found in 15-20% of patients with pulmonary TB.[1]

The NPTCCD, has reported a very low rate of GUTB in Sri Lanka. This may be due to lack of clear case definition, deficiencies in diagnosing, reporting and documentation.

6.2 Pathology

GUTB usually results from blood stream spread of *M. tuberculosis* from the lungs.[2] This happens after the initial pulmonary inoculation. Generally, GUTB is rare in children and young adults. The bacillus infects one kidney and the disease progresses slowly.

There is slow destruction of renal parenchyma with cavitation, abscess formation, fibrosis and calcification. Fibrosis leads to calyceal deformities, obstruction and scarring.

Rarely, it produces a diffuse glomerulonephritis with acute renal functional impairment.

Generally, the symptoms of renal involvement are minimal. If not identified and treated, the disease would spread down along the ureter into the bladder.

The ureteric involvement and fibrosis lead to ureteric stenosis and stricture formation particularly at the vesico-ureteric junction and pelvi-ureteric junction.

Once the bacilli enter the bladder, the inflammatory process starts and leads to storage (irritative) urinary symptoms (e.g., frequency, nocturia, and urgency), lumbar pain and haematuria. If it is still not treated, the bacilli ascend the contralateral ureter up to the other kidney.

6.2.1 Pathogenesis: GU TB male

Epididymal TB is almost a separate entity and the organisms usually reach the epididymis via the bloodstream. Therefore, in most instances, epididymal TB is an isolated finding without urinary tract involvement. Few cases of epididymal TB have been reported where the infection

occurred by direct retrograde spread of the organism or via lymphatics from the urinary tract. But these modes of spread are rare. Most patients with epididymal TB have a normal testis as the testicular involvement is rare. Therefore, even afterthe vasal involvement and blockage causing subfertility, sperms can be retrieved from the testis for the purpose of in vitro fertilization. Since the obstruction is close to the epididymis, reconstruction is difficult and results are poor. Spread of the organism to the prostate is also via the bloodstream in most patients.

The transmission of genital TB from male to female is very rare. Occasional reports of pelvic TB in the sexual partner of patients with epididymalTB suggest the possibility of female to male sexual transmission. TB of the penis is rare.

Figure 6: Transmission of TB to genital organs through bowel and aerosol inhalation

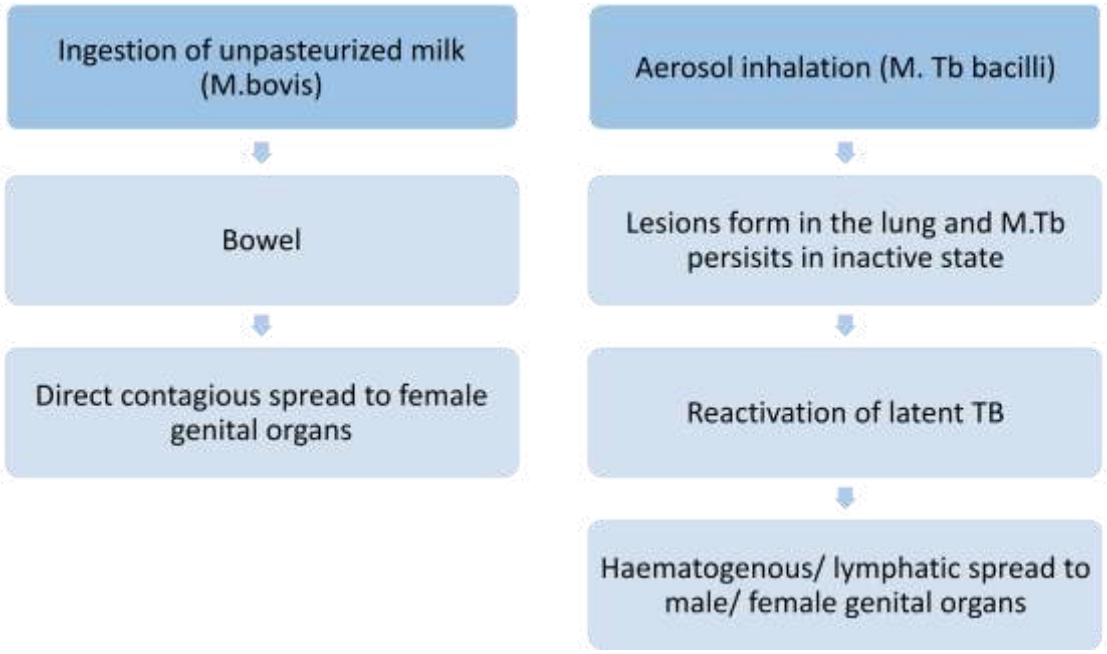
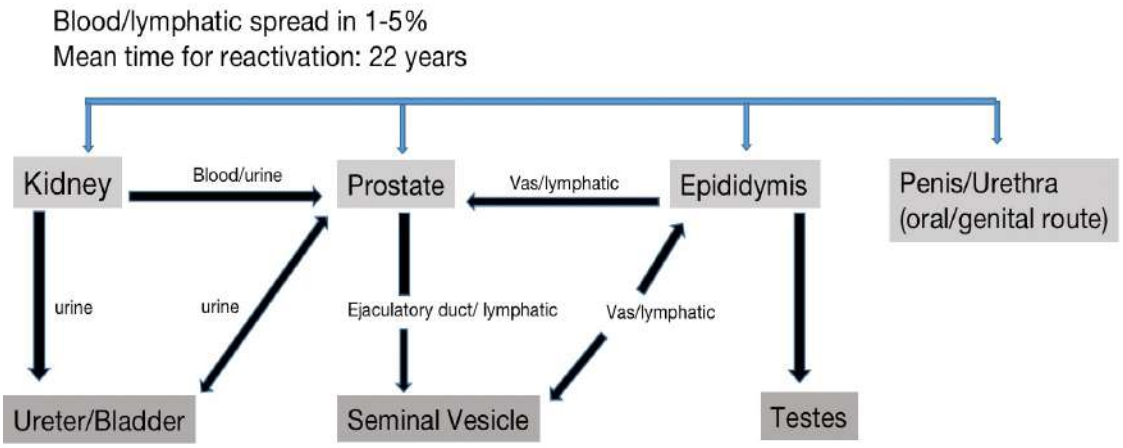


Figure 7: Spread of TB in males



6.2.2 Pathogenesis: GU TB Female

TB bacilli infect the female genital tract by four routes - haematogenous route (with lungs as the common primary focus), descending direct spread (from infected pelvic organs), lymphatic spread (usually if the primary is in the abdominal cavity) and rarely as primary infection of the genitalia through sexual transmission.

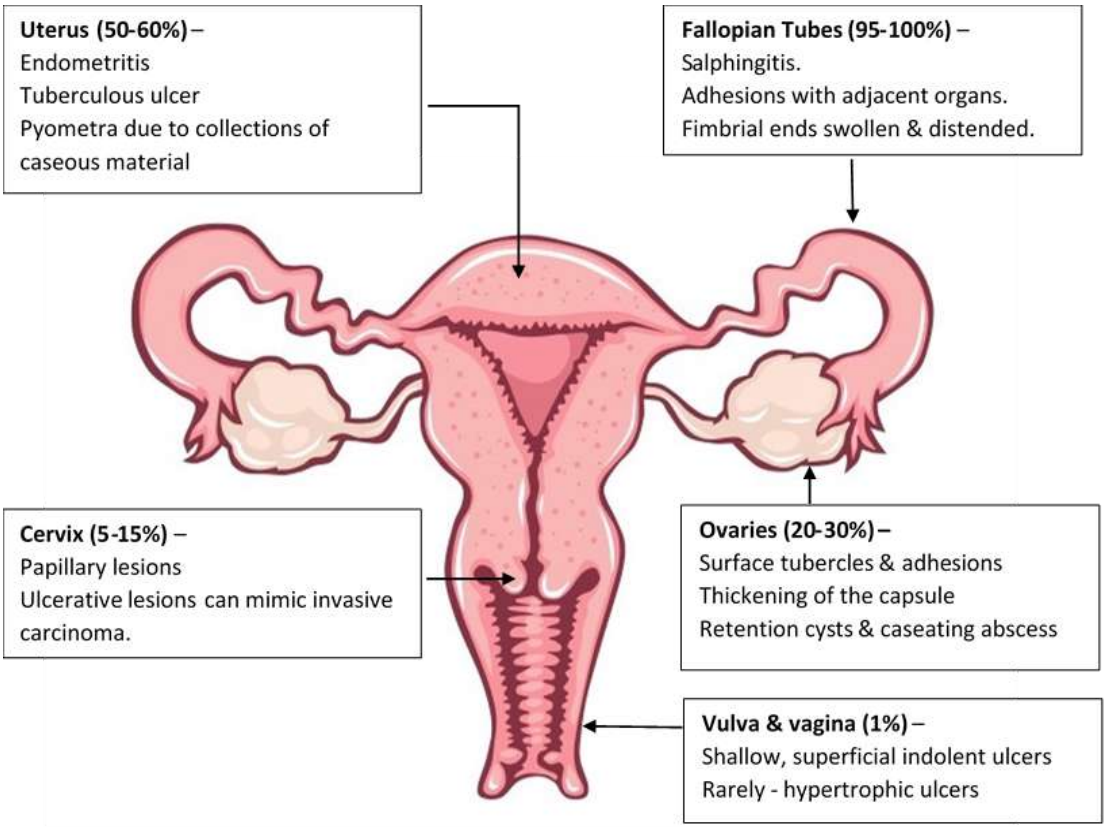
Rarely, when pelvic disease is secondary to TB peritonitis or if primary focus in lymph nodes/ bowel, the bovine bacillus – *Mycobacterium tuberculosis bovis* is likely to be involved. In all the other cases, generally the human bacillus – *Mycobacterium tuberculosis* is involved.

Usually, female genital TB starts at the tubes, following bloodstream spread, which begins in the submucosa at the outer ends and progresses inwards. The tuberculous infection spreads to the uterus and ovaries by direct extension. Extension to the uterus is along the endometrium and rarely into the myometrium.

The cervix is involved by spread from the endometrium or as part of the hematogenous infection. Tuberculous infection of the vagina and vulva may follow injury or abrasions to these structures in the presence of tubercle bacilli from the upper genital tract, intestinal tract, or lungs.

The finding of endometrial TB almost always means the tubes are affected, but tuberculous salpingitis can exist without associated endometriosis or ovarian involvement.

Figure 8: Sites of TB in female genital tract



6.3 Clinical features

The clinical diagnosis of GUTB in early stages of disease will be challenging astheir symptoms can be non-specific.

Tuberculous infection in the past as primary pulmonary TB or extra-pulmonaryTB gives an important diagnostic guide for GUTB. These patients may have contact history of TB. Recurrent urinary symptoms not responding to antibacterial treatment associated with haematuria is a common presentationof GUTB.

Tuberculous involvement of the epididymis presents as a solid mass in the scrotum. The commonest lump related to the epididymis is the epididymalcyst which is soft, fluctuant and trans illuminant. In most cases the testis can be felt separately and is normal. The longstanding, tuberculous epididymitis may rarely progress to sinus formation.

Constitutional symptoms like night sweats, evening pyrexia and malaise can be the presentations in GUTB. The common age group where GUTB is 20-55 years. In this age group,

the presence of vague, long standing urinary symptoms for which there is no obvious cause should raise the suspicion of GUTB.

Persistent pyuria is characteristic of GUTB. Partially treated urinary tract infections with or without bladder outlet obstruction and urolithiasis are the common causes of sterile pyuria. However, GUTB needs to be considered for persistent pyuria after bladder outlet obstruction leading to recurrent urine infections and urolithiasis are excluded.

Up to 20% of patients with GUTB may not have any leucocytes in the urine.

Table 7: Signs and symptoms of Genito Urinary TB in females

Urethra	• Urethral pus discharge • Voiding LUTS • Urine leak	• Urethral induration • Urethro-cutaneous fistula • Watering-can perineum • Inguinal lymphadenopathy
Fallopian tubes	• Infertility	• Blocked or fibrosed tubes • Salphingitis
Uterus	• Postmenopausal bleeding • Oligomenorrhoea • Menorrhagia • Abnormal vaginal discharge	• Pyometra • Persistent leucorrhea
Cervix	• Abnormal vaginal discharge • Postcoital bleeding	• Cervical erosion • Cervicitis
Ovary	• Adnexal mass • Chronic lower abdominal pain	• Tubo-ovarian abscess • Oophoritis
Vulva & Vagina	• Abnormal bleeding • Abnormal vaginal discharge	• Vaginitis • Ulceration

Table 8: Signs and symptoms of Genito Urinary TB in males

ORGAN	SYMPTOMS	SIGNS
KidneyUreter	• Haematuria • Chyluria • Flank pain • Symptoms of Renalfailure	• Flank mass, Sinus • Hypertension • Odema, Anemia
Bladder	• Storage LUTS (Urgency, Frequency, Hesitancy) • Dysuria • Suprapubic pain • Haematuria • Recurrent UTI	
EpididymisTestis	• Scrotal pain, • Scrotal pus discharge • Infertility • Testicular swelling	• Hard nodularEpididymis • Indurated enlargedtestes • Scrotal odema, sinus • Hydrocele
Prostate	• Frequency, Nocturia • Dysuria • Haematuria • Haematospermia • Pelvic pain	• Irregular NodularProstate • Fluctuant Prostate • Perineal sinus
Vas-Deferencee Seminal Vesicle	• Low ejaculate volume • Infertility • Haematospermia	• Beaded Vas • Calcified seminalvesicle
Penis	• Papular, plaques(Lupus vulgaris) • Mass, ulcer • Erectile dysfunction	• Penile nodule, Ulcer

6.4 Investigations

6.4.1 Microbiology and laboratory diagnosis

A microbiologic diagnosis of TB is made by isolation of the organism from urine or biopsy material on conventional solid media. Detection of acid-fast bacilli from urine samples by Ziehl-Neelsen stain is not reliable to make a definitive diagnosis due to the possible presence of *M. smegmatis* which are acid-fast bacilli too. However, it helps to screen suspected cases.

At least three (some even suggest five) early morning full voided urine samples, should be sent for examination. For the acid-fast bacilli to be positiveat least 10,000 bacilli/ ml should be present in urine. Since GUTB is a pauci-bacillary disease, false negatives with urine microscopy are common.

Culture of *M. tuberculosis* from urine or biopsied tissues is the gold standard in diagnosis of GUTB. The traditional methods take 6 weeks to yield results (LJ or Dubos media).

In a patient being evaluated for GUTB, Quinolones (e.g., ciprofloxacin) can destroy the *M. tuberculosis* and should be avoided during the period when urine samples are collected.

Nucleic acid replication techniques such as PCR are used commonly to detect *M tuberculosis* in urine. Few studies done specifically to evaluate the success of PCR in detecting mycobacterial DNA in urine have shown satisfactory sensitivity and specificity. Though the reported sensitivity and specificity rates of around 60% are good enough when compared with other tests to diagnose GUTB, clinicians who have to take decisions on individual patients may not be happy with these rates.

Ureteral catheterization can be used to collect urine samples for culture from each kidney and the yield rates may be higher than ordinary voided samples.

6.4.2 TST

A positive tuberculin test should be used with the clinical and radiological evidence, to support the diagnosis of GUTB. A negative tuberculin test should not exclude a diagnosis of GUTB. In many epididymal TB cases the Mantoux test is negative.

Utilization of IFN-γ assays provides immunological evidence for TB exposure. This is useful in immunocompromised patients (e.g.,end-stage renal disease, post-transplant patients) as the

TST may be false negative. Positive IFN-γ assay results (QuantiFERON TB Gold test and ELISPOT) may help the diagnosis of GUTB in such patients.

6.4.3 Radiology

Plain X-ray KUB is useful in patients with calcifications. Any unusual pattern of calcification should raise the suspicion of GUTB. Calcification of the renal parenchyma develops in about 25% of patients with renal TB. Calcification due to TB is ill-defined, diffuse and does not fit into any pattern. Calcification does not mean inactive infection and needs proper evaluation and treatment.

In spite of newer radiological investigations like ultrasound, CT scan and MRI, CT Intra Venous Urography (CT IVU) continues to be the key investigation in the diagnosis of GUTB. Approximately 90% of patients with urinary tract TB cause abnormalities in theCT IVU.

Renal lesions may appear as distortion of a calyx, as a calyx that is fibrosed and completely occluded (lost calyx), as multiple calyceal deformities or as severe calyceal or parenchymal destruction and non-visualized kidneys. The IVU imaging will demonstrate ureteric strictures when present. The cystogram is important in defining the changes in the bladder such as small capacity, irregular outline or vesicoureteric reflux.

Ultrasonography may detect changes associated with parenchymal involvement (e.g., calyceal dilation, cavities) but its main role is in percutaneous nephrostomy in obstructed kidneys due to ureteric stenosis.

CT is helpful in identifying small intrarenal lesions (scarring, masses and cavities) and auto-nephrectomy. Retrograde uretero-pyelography is useful to delineate the site and length of a ureteric stricture.

Hysterosalpingography (HSG) evaluates the internal structure of the female genital tract and tubal patency. Presentation of TB can be tubal occlusion, tubal dilatation and specific patterns including, ‘cotton wool plug’, ‘beaded tube’, ‘pipestem tube’ etc. TB should be strongly suspected in the presence of synechiae, tubal obstruction in the transition zone between the isthmus and ampulla, calcified lymph nodes, irregular linear or nodular calcifications in the adnexal area.

High-resolution abdominal and transvaginal ultrasonography may demonstrate loculated ascites; bilateral, predominantly solid, adnexal masses containing scattered small calcification; thickened omentum; thickened peritoneum; and endometrial involvement, which might alert the clinician to suspect genital tract TB.

6.4.4 Cystoscopy

Cystoscopy will show extensive inflammatory changes in the bladder in the presence of tuberculous cystitis. Late cases show the classical 'golf hole' ureteric orifice due to scarring and contraction. However, bladder biopsy is to be avoided in the presence of tuberculous cystitis.

6.4.5 Biopsy and histopathology

Biopsy material should be sent for histology in formal saline. Specimen for Xpert MTB/RIF Ultra and cultures should be sent in normal saline.

In female genital TB, histologic examination of endometrial tissues removed bybiopsy or curettage, especially from the cornual area, affords a rapid method of diagnosing genital TB. This can be performed using hysteroscopy and targeted biopsy, followed by dilation and curettage which increase the yield onendometrial specimens merely by increasing the amount of tissue available forhistologic evaluation and cultures.

6.4.6 Laparoscopy in Female GU TB

Laparoscopy is an invasive procedure and provides visual inspection of the ovaries, fallopian tubes, peritoneal cavity and biopsy of the tuberculous lesions. The laparoscopic findings may vary from normal appearance to tubercles on the surface, fimbrial block, fimbrial phimosis, tubal beading, peri-tubal adhesions, periovarian adhesions and tubo-ovarian mass.

6.5 Treatment

6.5.1 Pharmacological treatment

Since GUTB is a pauci-bacillary form of TB, a six-month course of antituberculous drugs is adequate. INH, Rifampicin, Ethambutol and Pyrazinamide are given for the initial two months (intensive phase). INH and Rifampicin are given for the next 4 months (continuation phase). In complicated cases (e.g., recurrence of TB, HIV infection, immunosuppression) longer courses (9-12 months) are recommended.

Special considerations apply to the treatment of TB in patients with renal impairment. Rifampicin, INH and Pyrazinamide can be given in normal dosage. These are eliminated in the bile or broken down to metabolites that are not excreted by the kidney. Dose adjustment according to the Glomerular Filtration Rate (GFR) is required in the use of Ethambutol. It is widely excreted by the kidneys.

Steroid Therapy

Routine use of steroids is not indicated in GUTB. Use of steroids is important in severe bladder symptoms, and tubular structureinvolvement (e.g., ureter, fallopian tubes, spermatic code).

High dose prednisolone (ie, at least 1mg/kg/BW) for 4-6 weeks is recommended, because Rifampicin reduces effectiveness and bioavailability ofprednisolone by 66%.

6.5.2 Surgical treatment

Although chemotherapy is the mainstay of treatment, about 50% of patients with GUTB will require some form of surgical intervention at some stage of thedisease. Surgical intervention would be ablative surgery or reconstructive surgery.

The ablative surgery may be necessary in the initial management of GUTB to control sepsis or to treat abscesses. Nephrectomy is indicated if there is uncontrollable urinary tract sepsis, expanding calcification and hypertension attributed to the diseased kidney. Almost all these are non-functioning kidneys. Main forms of reconstructive surgery are ureteric reimplantation (after excision of stricture) and bladder augmentation (for a small fibrotic bladder).

Both ablative and reconstructive surgical procedures are recommended to be done after about 4 weeks of drug treatment within the intensive phase. Early ureteric stenting or percutaneous nephrostomy may be indicated if the kidneyis obstructed and patient has not yet completed 4 weeks of treatment.

The ureteric strictures are commonly situated in the lower end at the uretero-vesical junction. It can occur in the upper end or in the mid ureter lesscommonly.

In female genital TB, as the disease is usually remarkably localized and accessible, excision of the affected area can be done. If the disease is widespread, the operation of choice is total abdominal hysterectomy with bilateral salpingo-oopherectomy followed by hormone replacement therapy, especially in a premenopausal woman. If the patient is premenopausal

andthe ovaries look normal, they may be conserved. Surgery is indicated in persistent and recurrent disease despite adequate treatment, persistent non healing fistula and multidrug resistant disease. However, over treatment with radical surgery should be avoided all the time especially when the patient is young.

6.6 Follow up

M. tuberculosis is an organism with very destructive capabilities. Its destructive nature is slow but long standing. Even after making the urine free of organisms, tissue fibrosis and scarring may progress. Hence these patients with GUTB should be followed up carefully to identify the complications secondary to persisting tissue fibrosis.

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Chapter 7: TUBERCULOUS LYMPHADENOPATHY

7.1 Introduction

Lymphadenitis is the commonest form of EPTB accounting for 35 % of all EPTB.

It is both a diagnostic and a therapeutic challenge because it mimics other pathological processes, yields inconsistent laboratory findings and shows unpredictable behavior during treatment. This is further compounded by the occurrence of TB lymphadenitis due to MOTT occurring mainly in children and in HIV positive patients. Most MOTT species are resistant to standard anti-tuberculous medication and treatment regimens differ.

Cervical lymph nodes are the most common site of node involvement and reported in 60% to 90% patients with or without involvement of other lymphoid tissues. Cervical lymphadenitis, which is also referred to as scrofula, may be a manifestation of a systemic tuberculous disease or a unique clinical entity localized to the neck.

7.2 Pathogenesis

TB lymphadenitis may occur during primary tuberculous infection or as a result of reactivation of dormant foci or direct extension from a contiguous focus.

Primary infection occurs on initial exposure to tubercle bacilli when Inhaled droplet nuclei are small enough to pass through muco-ciliary defenses of the bronchi and lodge in terminal alveoli of the lungs. The bacilli multiply in the lung forming a Ghon focus. The lymphatics drain the bacilli to the hilar lymph nodes. The Ghon focus and related hilar lymphadenopathy form the primary complex. The infection may spread from the primary focus to regional lymph nodes. From the regional nodes, organisms may continue to spread via the lymphatic to other nodes or may pass through the nodes to reach the blood stream~~,~~

Hilar, mediastinal and paratracheal lymph nodes are the first sites of spread of infection from the lung. Supraclavicular lymph node involvement may also reflect lymphatic drainage routes from the lung.

Cervical tuberculous lymphadenitis may represent spread from the primary focus of infection in the tonsils, adenoids, Sino-nasal region or osteomyelitis of the ethmoid bone. In untreated primary TB of children, enlargement of hilar and paratracheal lymph nodes (or both) becomes apparent on chest radiographs.

In the early phase of superficial lymph node involvement, progressive multiplication of *M. tuberculosis* occurs. The onset of delayed hypersensitivity is accompanied by marked hyperemia, swelling, caseative necrosis of the center of the nodes. This can be followed by inflammation, progressive swelling and matting with other nodes within a group. Adhesion to the adjacent skin may result in induration and purplish discoloration. The center of the enlarging gland becomes soft and caseous material may rupture into surrounding tissue or through the skin forming sinuses.

The lymphadenitis due to NTM is contracted from the environment by ingestion, inhalation, inoculation etc. The portal of entry for NTM may be the oral mucosa or gingiva. This is particularly important in children, because deciduous teeth may harbor the NTM that may reach the neck sites around the mandible through the lymphatics.

7.3 Clinical presentation

Mycobacterial infection should be considered in the differential diagnosis of a cervical swelling, especially in endemic areas. The duration of symptoms before diagnosis may range from a few weeks to several months. It may present as a unilateral single or multiple painless slow growing mass or masses developing over weeks to months, mostly located in the anterior and posterior cervical and less commonly in the supraclavicular region. A single node especially in the jugulodigastric triangle is likely to be NTM lymphadenitis.

Fistula formation is seen in nearly 10% of the mycobacterial cervical lymphadenitis. Cervical nodes in the submandibular region are most commonly affected in children. Young children, more often present with only one lesion and the referring physician more frequently suspects a neoplasm, bacterial adenitis or reactive adenopathy.

In *M. tuberculosis* lymphadenitis, up to 57% of patients have no systemic symptoms. Some patients may present with low grade fever, weight loss and fatigue and less frequently with night sweats. Cough is not a prominent feature of tuberculous lymphadenitis. Multiplicity and matting are important findings of tuberculous lymphadenitis.

Clinical features depend upon the stage of the disease. The lymph nodes are usually not tender unless with (i) secondary bacterial infection, (ii) rapidly enlarging nodes or (iii) coexisting HIV infection.

The lymph node abscess may burst infrequently leading to a chronic non-healing sinus and ulcer formation. Classically, tuberculous sinuses have thin, bluish, undermined edges with scanty watery discharge. Scrofuloderma is a mycobacterial infection of the skin caused by direct extension of TB into the skin from underlying structures.

Worldwide data suggest that about 10% of the patients have a risk factor for the development of TB adenitis, diabetes, HIV or immunosuppressive drugs.

7.4 Differential diagnosis

The differential diagnosis of isolated peripheral lymphadenopathy is extensive and includes malignancy (e.g., Hodgkin lymphoma and non-Hodgkin lymphoma) and other nontuberculous mycobacterial infections (e.g., *M. scrofulaceum, M. avium* complex, *M. Kansasii*], cat scratch disease, fungal infection, toxoplasmosis, sarcoidosis, bacterial adenitis, and brucellosis. Kikuchi's disease can cause a necrotizing lymphadenitis and mimic tuberculous cervical lymphadenopathy.

The most likely alternative diagnoses depend on the clinical setting including the patient's age, immune status, and presenting clinical features.

Diagnosis

A high index of suspicion is needed for the diagnosis of mycobacterial cervical lymphadenitis.

7.4.1 FNAC Smears of lymph nodes

Smears can be obtained either from a draining sinus or by Fine Needle Aspirate Cytology (FNAC). Ziehl-Neelsen staining of the smears may reveal mycobacteria in the fresh specimens. Chances of finding AFB is higher in patients with cold abscesses

The sensitivity and specificity of FNAC in the diagnosis of tuberculous lymphadenitis are 60% and 96%, respectively. Clusters of epithelioid cells (sometimes called epithelioid histiocytes) give rise to formation of granulomas. TB granulomas are usually large, 400 μm in maximum dimension with caseation and bands of epithelioid histiocytes in the periphery. Epithelioid cells fuse to form Langhans giant cells which are seen more towards the center. A peripheral rim of lymphocytes may also be seen. Neutrophilic infiltration and hemorrhage may occur.

Numerous neutrophils favor an alternative diagnosis while neutrophils in areas of necrosis, serpentine Langham's giant cells, micro-abscesses, favor an infection with MOTT.

Cytomorphology of tuberculous lymph node aspirates reveals caseative type granular necrosis in 92 % cases, epithelioid cells in 85 % cases and AFB positivity in 13 % cases The incidence of AFB positivity in patients of tuberculous lymphadenitis was highest with the cytological picture of necrosis, polymorphs and lymphocytes i.e. 29 %.

The finding of caseative necrosis, with or without granulomas and or Langhans cells is highly consistent with TB especially in endemic areas together with clinical and other ancillary tests, even though bacilli are not detected on AFB stain.

The relationship between the presence of granulomas and AFB positivity is inverse. Irrespective of the specimen being FNAC or biopsy the yield on Ziehl Neelsen stain is around 25%.

7.4.2 Ultrasound scan guided FNA

Ultrasound of the neck can demonstrate single or multiple hypoechoic and multiloculated cystic lesions that are surrounded with thick capsules US guided FNA has been shown to have an increased diagnostic yield.

Recommendations for Ultrasound scan guided FNA

In those whom FNA is inconclusive, a repeat FNA or better still FNA under US guidance is recommended. FNAC is a sensitive, specific and cost-effective way to diagnose mycobacterial cervical lymphadenitis, especially in children presenting with a suspicious neck swelling.

Combination of FNAC with culture or a Mantoux test further increases the diagnostic yield in mycobacterial cervical lymphadenitis.

7.4.3 Histopathology of excision biopsy of lymph nodes

Lymph node biopsy/excisional biopsy for histopathologic (sent in 10% neutral buffered formalin) and microbiological evaluations (sent in normal saline) has the highest diagnostic yield (90%) and should be pursued, in cases where fine needle aspiration is not diagnostic.

Histopathologic examination is diagnostic of mycobacterial cervical lymphadenitis. Langerhans giant cells, caseative type necrosis, granulomatous inflammation and calcification can be seen.

The presence of micro abscesses, ill-defined granulomas, non-caseating granulomas and a small number of giant cells is more prominent in nontuberculous adenitis when compared with tuberculous adenitis.

Recommendations for Histopathology of excision biopsy of lymph nodes

Incision biopsy is not recommended, as this can result in sinus formation and poor healing. Biopsies should always be excision biopsies. In addition to histopathological examination, biopsy material should always be sent in normal saline for mycobacterial culture.

7.4.4 Culture

Culture of mycobacterium is diagnostic of mycobacterial cervical lymphadenitis. However, a negative culture result should not exclude the diagnosis of mycobacterial cervical lymphadenitis. Different media can be used to culture the mycobacteria (L-J, Middlebrook, and Bactec TB). However, several weeks are needed to obtain the culture result. Cultures are positive in 20%-80%% of the cases. Presence of neutrophilic inflammation and necrosis correlate with culture positivity,

7.4.5 TST

False-negative reactions can occur in about 20% of all persons with active TB. The tuberculin test is considered diagnostic in mycobacterial infections, though its value in diagnosing disease is debated.

In mycobacterial cervical lymphadenitis cases the test may be positive (49%), intermediate (36 %) or negative (15%).

Recommendations for TST

The TST is positive in the majority of patients with TB lymphadenitis (in the absence of HIV infection), positive TST is not sufficient to establish the diagnosis. A negative TST is not helpful in excluding the diagnosis, especially in immunosuppressed individuals.

A positive reaction of > 10mm which would favor lymphadenitis due to MTB than due to MOTT.

7.4.6 Molecular Testing with Xpert MTB RIF /RIF Ultra

Xpert MTB/RIF Ultra is a fast and useful technique for the demonstration of mycobacterial DNA fragments in patients with clinically suspected mycobacterial lymphadenitis. The presence of few dead or live microorganisms is enough for Xpert positivity. The Xpert MTB/RIF Ultra can be applied on the materials obtained by FNA and can reduce the necessity for open biopsy.

Its sensitivity ranges between 43% and 84%, and its specificity between 75% and 100%. PCR can be applied when smears and cultures are negative. PCR is a confirmatory and sensitive technique for the diagnosis of mycobacterial cervical lymphadenitis. Xpert testing will give negative results in infections caused by MOTT. It is used as an adjunct to conventional techniques in the diagnosis of mycobacterial infections.

Recommendations for Molecular Testing with Xpert MTB/RIF Ultra

Xpert MTB/RIF Ultra has a sensitivity that ranges between 43% and 84%, and its specificity is between 75% and 100%; It can differentiate between MTB and MOTT infections. Presence of DNA fragments from dead bacilli can give a positive result.

The Xpert MTB/RIF Ultra should be reserved only for problematic cases

7.4.7 Radiology and imaging

Chest radiograph, ultrasound, CT and MRI of the neck can be performed in mycobacterial lymphadenitis. In TB lymphadenopathy, associated chest lesions on chest radiography are commonly seen in children, but less common in adults. Abnormal chest radiograph is seen in up to 10 % of adenitis patients and one half of these patients may have positive microbiological evidence of pulmonary TB.

Ultrasound of the neck can demonstrate singular or multiple hypoechoic and multi-loculated cystic lesions that are surrounded with a thick capsule.

In CT, the presence of conglomerated nodal masses with central hypo density, a thick irregular rim of contrast enhancement and inner nodularity, a varying degree of homogeneous enhancement in smaller nodes, dermal and subcutaneous manifestations of inflammation, such

as thickening of the overlying skin, engorgement of the lymphatics and thickening of the adjacent muscles, and a diffusely effaced fascial plane may suggest mycobacterial cervical lymphadenitis. However, these findings may also be seen in other diseases like lymphoma and metastatic lymphadenopathy.

CT can be a useful tool to distinguish between TB lymphadenitis and lymphoma. In patients with lymphoma, lower para-aortic node involvement is more common. TB more often involved upper para-aortic, lesser omental, mesenteric, and anterior para-renal lymph nodes. Peripheral enhancement (often with a multilocular appearance) was also a feature of TB lymphadenopathy; homogeneous attenuation was more common in the setting of lymphomatous adenopathy.

MRI may reveal discrete, matted and confluent masses. Necrotic foci, when present, are more frequently central than peripheral, and this together with the soft tissue edema may be of value in differentiating mycobacterial cervical lymphadenitis from metastatic nodes. If the cervical mass is necrotic, there will be low and high signal intensity in the center of the mass in T1- and T2-weig-ted images, respectively.

7.4.8 Bronchoscopy

In the setting of isolated intrathoracic lymphadenopathy, bronchoscopy or endo bronchial ultrasonography may be useful to establish a diagnosis of TB if sputum studies are negative.

Mediastinoscopy with biopsy is indicated in assessing isolated mediastinal nodal involvement.

7.4.9 Other investigations

- Patients with suspected or proven TB should undergo HIV testing.
- All patients with suspected TB lymphadenitis should have a chest radiograph to rule out concomitant pulmonary TB and to assess mediastinal nodes.
- US is an inexpensive useful mode of imaging in patients with cervical lymphadenopathy. It can also provide a guide for FNA and can assess nodes in follow up. US should be used where available for assessment of cervical lymphadenopathy.
- CT or MRI is useful in assessing mediastinal and abdominal node involvement when these are suspected.

7.5 Treatment

ATT is the mainstay in the management of TB lymphadenitis. First-line drugs are INH, Rifampicin, Ethambutol, Pyrazinamide are given daily during 2 months of intensive phase and INH and Rifampicin for a further 4 months of continuation phase.

With treatment, reduction of size of the lymph nodes swelling without complications may occur in 70-90% of patients. Early institution of specific ATT and close clinical monitoring for adverse drug reactions and disease regression are the key factors for successful management.

7.5.1 Paradoxical reaction (PR)

Antimycobacterial therapy may prompt a PR or increase in lymph node size and/or enlargement of additional lymph nodes during or after cessation of treatment. This is attributable to an immune response to dying *M. tuberculosis* organisms. Enlargement is experienced usually in about 2 to 3 months in to treatment and with continued treatment it may take up to 4 months to resolve. Clinical manifestations may include lymph node enlargement (12 %), fluctuance (11 %), overlying erythema and/or spontaneous discharge (7 %).

Repeated FNA with AFB smears and culture helps to differentiate true bacteriological relapse from immunological reactions. TB PCR helps to differentiate MTB from MOTT.

In few cases even after treatment FNAC may remain positive for tuberculosis and even for AFB because of dead bacilli. Therefore, treatment in such cases should be given in culture-positive cases only.

7.5.2 Corticosteroids

Systemic steroids have been shown to reduce inflammation during the early phase of therapy for lymph node TB and may be considered if a node is compressing a vital structure i.e. bronchus or in diseases involving a cosmetically sensitive area.

Prednisolone, 0.5mg/kg per day for 4 weeks followed by gradual tapering over the next 4 weeks, along with appropriate chemotherapy is adequate. However, the safety and utility of this approach remains largely unproven except in intrathoracic disease where it was found to relieve the pressure on the compressed bronchus.

When steroids are used for cosmetic reasons, a lower dose and a shorter duration may be appropriate.

7.6 Difficulties in managing lymph node TB

Apart from difficulties encountered in diagnosis of lymph node TB, certain problems may be encountered during its treatment.

These include;

1. Appearance of freshly involved nodes
2. Enlargement of the existing nodes
3. Development of fluctuation
4. Appearance of sinus tracts
5. Residual lymphadenopathy after completion of treatment
6. Relapses

Possible explanations of these responses to therapy in lymph node TB include:

1. Enhanced delayed hypersensitivity reaction in response to mycobacterial antigens released during medical treatment of the disease
2. Co- existence of additional pathology such as lymphomas and HIV etc.
3. Disease caused by MOTT
4. Unidentified drug resistance

7.7 How to overcome difficulties in managing lymph node TB?

Proper assessment before diagnosis, evaluation and close monitoring during treatment are the keys to success in the management of lymph node TB.

A suggested management plan would be as follows;

1. Record all the possible sites of involvement, nature and size of the involved lymph nodes at the inception of treatment.

2. Identify any co-existing disease like HIV, lymphoma and manage appropriately. Repeat FNAC or excision biopsy may be required.

3. Most nodes that enlarge during therapy or appear afresh will ultimately respond to treatment. Only close follow up is required in these patients.

4. Appearance of fluctuation in one or more lymph nodes calls for aspiration under aseptic precautions.

7.8 Indications for surgery

When the nodes are not responding to treatment and the cultures are negative, excision biopsy is indicated.

Surgical techniques include aspiration, incision and drainage, curettage, complete surgical excision of the affected lymph nodes and the overlying skin and selective nodal or functional neck dissection when required.

When lymph nodes are fluctuant and ready to drain, anti-gravity aspiration should be done. Aspiration, may result in 50% cure rate and can be performed when surgical options are limited. Curettage which may result in 70% cure rate, can also be done when the lesion is in proximity to a nerve or if there is extensive skin necrosis.

Lymph node excision is not usually indicated. Surgery increases the cure rate with excellent cosmetic results and a low complication rate. Antibiotics are used to augment surgical therapy.

Simple incision and drainage are associated with prolonged postoperative wound discharge and hypertrophic scarring. Excision of the skin overlying the mass can be performed when there is a fistula, scar formation, or necrosis.

After completion of treatment, residual lymph nodes should be observed closely. Any increase in size or appearance of symptoms calls for excisional biopsy for histopathology and culture. Most of these patients will respond to retreatment with the same regimen.

All efforts should be made to isolate the causative agent and to obtain prompt sensitivity testing, particularly in relapsed cases and non-responders where treatment is modified accordingly.

7.9 TB lymphadenitis in HIV infected patients

Among patients with TB lymphadenitis in the setting of HIV infection, there may be a significant mycobacterial load with concomitant systemic findings including fever, sweats, and weight loss. Abnormal chest radiograph is frequently observed, and such patients are more likely to have disseminated TB with lymphadenitis in more than one site.

Diagnosis of TB lymphadenitis is established by histopathological examination along with AFB smear and culture of lymph node material. The yield of FNA appears to be highest in the setting of HIV infection and in regions where the prevalence of TB is high.

Specimens should be submitted for microscopy, culture, cytology and Xpert MTB/RIF Ultra testing (wherever available). Xpert MTB/RIF Ultra testing is especially useful to exclude atypical mycobacterial infections in HIV positive patients.

Chest imaging should be pursued in the setting of suspected TB lymphadenitis. Many patients with tuberculous lymphadenitis have no evidence of active pulmonary TB on CXR; abnormalities have been described more frequently among patients with HIV infection in some series (see 'Imaging' above).

Those who are co-infected with HIV are more likely to develop PRs while on ATT. A similar phenomenon, seen in patients with HIV infection who begin concurrent antiretroviral therapy is a result of immune reconstitution.

7.10 Tuberculous lymphadenitis in children

Similar to adult's tuberculous lymphadenitis, in children also there is a wide range of differential diagnoses. Infection with MOTT is commoner in children than infection with *M. tuberculosis*. The initial focus of infection is decidual teeth which harbor MOTT.

Multiple matted nodes and sinus formation favor MTB even though Mantoux test would not show a positivity of more than 10 mm. Histologically non-caseating granuloma, stellate shaped Langerhans cells, micro-abscess and neutrophilic infiltration favors MOTT.

7.11 Tuberculous lymphadenitis, follow up after treatment

About 20 % of treated patients tend to have residual adenopathy at completion of treatment. Lymph nodes larger than 10 mm are considered significant. They need follow up and re biopsy, If the nodes start enlarging. Histology of granulomatous inflammation with caseation, positive Zeil Neelson stain or positive Xpert MTB/RIF Ultra can occur without having a true relapse. Retreatment is given only in culture positive cases. In rare instances, culture negative relapses have been reported. In such instances expert opinion is sought.

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Chapter 8: TRACHEOBRONCHIAL AND UPPER AIRWAYS TUBERCULOSIS

8.1 Upper airway tuberculosis

8.1.1 Introduction

Involvement of upper respiratory tract in tuberculosis (URT-TB) is especially seen in patients with a variety of risk factors, such as the presence of HIV infection, diabetes, smoking, alcoholism, drug abuse, malignancies, and use of immunosuppressive drugs. Laryngeal TB is the most common of all forms of upper respiratory tract TB and other areas of involvement include pharynx, tonsils, soft palate, nose, paranasal sinuses, middle ear, mastoid and tongue. The URT-TB is one of the rare forms of extrapulmonary TB.

8.1.2 Pathology

Lesions are ulcerative or nodular in appearance.

Table 9: Sites of Upper Respiratory Tract TB

Nose and nasopharynx
Nasal septum, nasal floor and vestibule, rarely alae nasi
Maxillary sinuses; rarely sphenoid sinus
Nasopharynx
Oral cavity
Tongue: tip, borders, dorsum, and base
Lips-rarely
Floor of mouth, soft palate, tonsils, anterior pillars of fauces, uvula
Oropharyngeal walls
Salivary glands
Eustachian tubes, middle ear, Mastoids
Larynx
Laryngeal walls: glottic and subglottic areas
Vocal cords

8.1.3 Clinical features

Clinical features of URT TB vary according to the site of the organ affected and concurrent pulmonary pathology is common.

8.1.3.1 Nasal TB

Nasal and paranasal sinus TB is an uncommon entity. Maxillary sinus is the mostly affected sinus. Patients with nasal and paranasal TB present with nasal obstruction and nasal discharge. They may present with epistaxis or blood-stained nasal discharge. A slowly growing, ulcerative lesion, may appear on the nasal vestibule, the nasal septum, and the alae. Some patients may develop external nodules, ulcers, or nasal deformity. Nasal septal ulceration leading to perforation of septal cartilage can occur.

8.1.3.2 Oral cavity and pharyngeal TB

Oral cavity and pharynx are rare sites of TB infection. Infection can spread from hematogenous spread or spread from sputum. Tongue is the most common site of the involvement and other sites include floor of the mouth, tonsils, soft palate, anterior pillars and uvula. Oral cavity lesions may appear as ulcers or nodules which can be single or multiple. Lesions may appear similar to malignant ulcers and may be painful or painless.

Nasopharynx is the commonest site of pharyngeal involvement and may present with nasal obstruction, rhinorrhea and adenoidal hypertrophy. Oropharyngeal TB may present with a painful throat. They may have laryngeal involvement and may present with a retropharyngeal TB abscess. Red and irregular pharyngeal mucosa and erythematous papules are usual presentations. Tonsil TB may present with throat pain, dysphagia and ulcerations.

TB involving middle ear and mastoids may present with multiple ear drum perforations, painless recurrent otorrhea and hearing loss. They may present with post auricular fistula and preauricular lymph node enlargement as cardinal features.

8.1.3.3 Laryngeal TB

Laryngeal TB is common among patients who are on steroid therapy (systemic or inhaled) and patients with HIV infection. Laryngeal TB may mimic laryngeal carcinoma. Most common symptoms of laryngeal TB are hoarseness of voice, cough, dysphagia, odynophagia, pain in

the throat, and referred pain in the ear. Patients may present with stridor and severe upper airway obstruction which may warrant emergency airway management. Endoscopic examination may show severe mucosal edema, ulcerations, nodules, abscess and polypoidal mass resembling malignancy. Laryngeal cartilage destruction may occasionally result from laryngeal-TB.

8.1.4 Diagnosis

Clinical examination of the upper airway with proper instruments will demonstrate the clinical features of suspected patients.

1. CXR need to be done in suspected patients to exclude pulmonary TB.

2. Flexible endoscopic examination of nose pharynx and larynx.

- Specimen collection including swab smear and biopsy under local anesthesia can be done while endoscopic examination. Diagnosis is achieved by histological and microbiological confirmation. Nuclear amplification test such as Xpert MTB/RIF Ultra are increasingly being used to detect TB for rapid diagnosis.

3. Direct laryngoscopy and biopsy

- For laryngeal TB, direct laryngoscopy and biopsy for proper histology and TB culture are the definitive diagnostic tools.
- Sputum microscopy is positive for only 20% of patients with laryngeal TB.
- A laryngeal swab smear positive for mycobacteria should not be considered diagnostic of laryngeal TB, because such swabs are frequently positive for patients with pulmonary TB, especially in children.
- Nuclear amplification test such as Xpert MTB/RIF Ultra are increasingly being used to detect TB for rapid diagnosis.

4. Mastoidectomy

Mastoidectomy and biopsy and TB culture of granulation tissue in clinically suspicious patients, can confirm the diagnosis.

5. Imaging (MRI/CT) will be useful in severe cases and poorly responding cases to exclude other pathologies.

8.1.5 Treatment

1. Standards treatment includes anti-TB chemotherapy for at least 6 months, modified on the basis of culture and sensitivity reports in cases of suspected drug resistance.

2. Systemic steroids therapy should be started early to prevent permanent scaring of tissue.

8.1.6 Follow up

Patients need to be followed up with clinical evaluation and repeat endoscopic evaluation.

8.2 Tracheobronchial TB

8.2.1 Introduction

TB infection involving tracheobronchial tree is not uncommon. Tracheobronchial TB is more common in females in their second and third decades of life. However tracheobronchial TB often faces delayed Diagnosis due to nonspecific clinical features and normal CXR in 10 to 20% of cases.

8.2.2 Pathogenesis

The pathogenesis of Tracheobronchial TB is unclear. However, it can be due to direct infiltration of disease from lungs;

1. Infected sputum and secretions causing direct implantation of the organism
2. Haematogenous spread
3. Lymphatic dissemination
4. Erosion of Lymph node into trachea or bronchus

Tracheobronchial TB has complex and varying clinical course which leads to clinical burden of bronchial stenosis.

8.2.3 Symptoms and signs of Tracheobronchial TB

1. Cough
2. Chest pain
3. Haemoptysis
4. Fever
5. Wheeze and Stridor

6. Dyspnea
7. Lethargy

Clinical Signs are heterogenous, and focal wheezing and reduced air entry can be found on auscultation.

Clinical signs and symptoms are often non-specific. Hence diagnosis of Tracheobronchial TB should be made on clinical findings, radiology, sputum and tissue analysis.

8.2.4 Diagnosis

CXR findings may be normal. However, if there is a distal segment obstruction, atelectasis of the distal pulmonary segment could be visible on CXR. Moreover, High-resolution computed tomography (HRCT) chest may show tree in bud appearance. Furthermore, CT thorax would yield more details such as stenosis and irregularities of airway and other features of TB. In addition, 3D reconstruction of the airway supports to estimate the extent of airway obstruction. Hence 3D reconstruction is helpful to plan further investigation such as Bronchoscopy and Biopsies.

Bacteriological confirmation is an important step in diagnosis and management. However diagnostic yield is not up to the expectation in direct sputum smear examination in tracheobronchial TB. Several studies have shown variable diagnostic yields from 17% to 79%. Higher yields are obtained by bronchoscopy guided specimens. Low direct smear diagnostic yield may be due to lack of ulcerations in the mucosal wall of the bronchus or difficulties with sputum expectoration.

Hence nuclear amplification test such as Xpert MTB/RIF Ultra are increasingly being used to detect TB and rapid diagnosis of Tracheobronchial TB.

Bronchoscopy is essential for accurate diagnosis of Tracheobronchial TB.

On the basis of Bronchoscopic appearance, Endobronchial TB is usually classified into 7 subtypes.

1. **Actively Caseating** —swollen hyperemic bronchial mucosa covered with whitish cheese-like material (figure 9)

2. **Edematous -hyperemic**—extensive mucosal swelling with surrounding hyperemia

3. **Fibrostenotic**—marked narrowing of the bronchial lumen with fibrosis

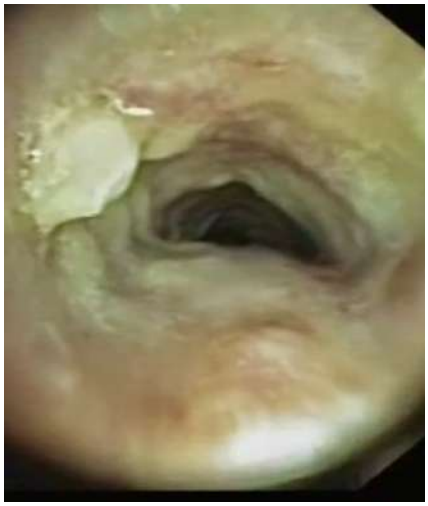
4. **Tumorous —**endobronchial mass with surface covered by caseous material and nearly totally occluding the bronchial lumen

5. **Granular —**appearance like scattered grains of boiled rice

6. **Ulcerative** —ulcerated bronchial mucosa

7. **Non-Specific Bronchitis** —only mild mucosal swelling and/or hyperemia

Figure 9: Swollen hyperemic bronchial mucosa covered with whitish cheese-like material



8.2.5 Clinical course and complications

All subtypes of endobronchial TB can be transformed to other subtypes between two extreme ends of healing and bronchial stenosis. Actively caseating and edematous hyperemic subtypes are known to have worse prognosis, resulting in fibro-stenosis in two third of patients. follow up bronchoscopy in 2 -3 months after starting treatment is recommended in most subtypes.

Bronchial stenosis and stricture formation are the commonest complications. These complications may develop in 60% to 95% cases despite adequate anti-TB treatment. Airway obstruction can occur in Tracheal stenosis. Bronchiectasis can occur in some patients which predominates in upper lobes and this can be further complicated with haemoptysis.

8.2.6 Management

Eradication of TB bacilli along with prevention of sequel is the primary goal of treatment in tracheobronchial TB. Treatment regimen consist of anti TB drugs for 6 months duration,

similar to pulmonary TB. It has been suggested that treatment with corticosteroids may be beneficial in preventing bronchial stenosis due to anti-inflammatory properties. However, the role of corticosteroids is still controversial in management of tracheobronchial TB.

Bronchial stenosis had been reported in spite of adequate chemotherapy in some patients. once stenosis has developed it is not possible to reverse with chemotherapy or steroids. Hence at this stage airway patency must be restored either by endobronchial interventions or surgical means.

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Chapter 9: TUBERCULOSIS OF ABDOMEN

9.1 Introduction

TB of the abdomen broadly refers to *Mycobacterium tuberculosis* infection that affects any of the organs in the abdominal cavity. Abdominal TB is arbitrarily defined to include infection involving the gastrointestinal tract, peritoneum, abdominal solid organs, and lymph nodes. The gastrointestinal tract is the most common site of involvement. According to the NPTCCD, Sri Lanka, 1995 cases of EPTB have been reported in 2022. TB of the intestine, peritoneum and mesenteric lymph nodes has been confirmed in 76 (8%) of them.

Because the signs and symptoms of abdominal TB are generally ambiguous, diagnosing the disease remains challenging for the clinician. The situation is further complicated by the low sensitivity and specificity of the diagnostic tests for abdominal TB. Invasive procedures like laparoscopy or laparotomy are frequently required to confirm abdominal TB. Hence, a high index of suspicion is crucial to shortening the time required for diagnosis and avoiding the major morbidity that may follow.

According to the literature, abdominal TB can be seen in any age group. In young patients, it can mimic inflammatory bowel disease, while in middle-aged and elderly patients, it can mimic cancer. The majority however, are between the ages of 21 and 40, with a male: female ratio of 1:1.

9.2 Pathophysiology

Gastrointestinal TB can develop as a primary infection without lung involvement or as a complication of active pulmonary disease. Sputum or infected milk can both introduce tuberculous bacteria into the digestive system. Due to the development of epithelioid tubercles in the lymphoid tissue of the submucosa, the bacilli can infect the mucosal layer of the GI tract. Caseous necrosis of the tubercles causes the underlying mucosa to ulcerate after approximately 2-4 weeks. This ulceration can eventually translocate to the deeper layers, the surrounding lymph nodes, and the peritoneum. Other routes include lymphatic channel spread or hematogenous spread from a tuberculous focus that originated elsewhere in the body to the abdominal organs. The infection may also spread from contiguous foci that are afflicted, such as a fallopian tube or a psoas abscess.

9.3 Clinical Features

The clinical symptoms of abdominal TB can vary depending on the form of the disease. Ascites, hepatomegaly, diarrhea, bowel obstruction, abdominal pain and/or distension and abdominal mass are a few examples.

The most frequent symptom of intestinal TB is abdominal pain, which can be brought on by peritoneal involvement, mesenteric inflammation or an obstruction of the intestinal lumen. Up to 30% of patients experience diarrhea, which may be caused by small or large intestinal involvement. Patients may frequently experience constitutional symptoms such as fever, malaise, night sweats, anorexia and weight loss. As the ileocecal region is the most common area of the intestine to be involved, a quarter of patients may have an abdominal mass in the right lower quadrant. There could be intestinal strictures and fistulas. Anal TB should be considered in the differential diagnosis of chronic or recurrent anal fistulas or abscess formation Evan though its rare.

The most frequent complication of abdominal TB is bowel obstruction, which can be brought on by adhesions or progressive stricturing. Gastrointestinal bleeding is uncommon and rarely serious. Potential causes of malabsorption include bacterial overgrowth in a stagnant loop, bile salt deconjugation and a reduced surface area for absorption as a result of intestinal ulceration.

Ascites, abdominal discomfort and fever are among the clinical signs of peritoneal TB (93%, 73%, and 58% respectively). Generally, it takes weeks or even months for the diagnosis to be made after the onset of symptoms. At the time of presentation, ascites is evident in more than 90% of patients with tuberculous peritonitis (pure ascites with no evidence of chronic liver cell disease is highly suggestive).

Hepatic TB can manifest as granulomatous hepatitis, intrahepatic growth or a hepatic abscess. Over 80% of cases of disseminated miliary TB involve the liver.

Involvement of the oesophagus, stomach, duodenum, pancreas and spleen is uncommon.

9.4 Diagnosis

All children and 50–80% of adults with abdominal TB have been found to be anaemic, and haematological tests generally show leukocytosis with relative lymphocytosis and an elevated ESR. Also common is Hypoalbuminemia is seen in most cases.

A CXR and sputum evaluation (if the patient is able to express sputum) for bacteriological confirmation of TB (smear, culture, or Xpert MTB/RIF Ultra), similar to other extrapulmonary TB infections, are crucial early diagnostic tests for individuals who are suspected of having abdominal TB or disseminated TB with abdominal involvement. According to literature approximately 15%-25% of cases with abdominal TB have concomitant PTB.

TST is positive in the majority of patients but has limited utility as a diagnostic tool because it cannot distinguish between active disease and previous sensitization. TBST and IGRA tests can also be used. These tests require an active immune response. Therefore, people who have immune suppression or chronic malnutrition as a result of their illness may have false negative results.

9.4.1 Imaging in abdominal TB

Radiological investigations are nonspecific, therefore have limited value. However, these investigations are helpful in narrowing down differential diagnosis and arranging further invasive investigations like laparoscopic or open biopsy procedure to confirm /exclude abdominal TB

9.4.2 Abdominal ultrasound

This would be routinely performed in suspected cases of abdominal TB. Ascites, simple or loculated, peritoneal, omental and bowel wall thickening, enlarged abdominal lymph nodes, liver and splenic lesions can be appreciated. However, it has only 63% sensitivity and similar specificity in diagnosing the disease.

9.4.3 Computed Tomography /MRI

Multi Detector Computed Tomography (MDCT) of the abdomen and pelvis post intravenous contrast administration is better in depicting the above lesions. Diffuse enhancement of the smooth peritoneal thickening, extent of lymph node involvement with central necrosis and peripheral rim enhancement could be better evaluated. In addition, MDCT could better depict segments of thickened bowel, liver and splenic lesions and suprarenal disease.MR imaging of the abdomen would give similar imaging findings and is recommended for patients with contraindications for IV contrast.

9.4.4 Endoscopy

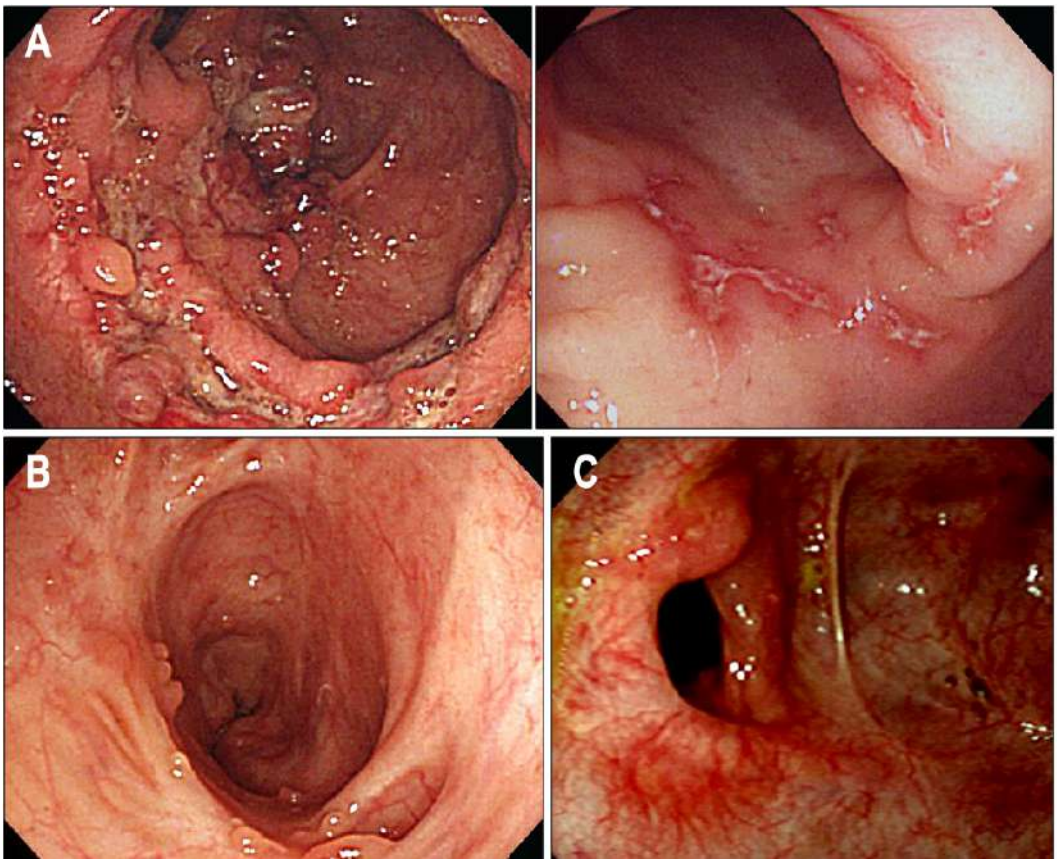
In suspected intestinal TB, a colonoscopy with biopsy is helpful to acquire histology and culture samples. Broadly, two types of intestinal lesions are predominant: ulcerative and hypertrophic. The former usually involves the small intestine and the latter, the ileocaecal region. The main differential diagnosis for intestinal TB on ileo-colonoscopy is Crohn's disease which also commonly involves the ileocaecal region. Differentiation is often challenging. Lesions may also mimic colonic carcinoma. A patulous ileocaecal valve with heaped-up folds, or a damaged valve with a “fish-mouth” gaping ileal opening, is more likely to be due to TB than to Crohn's disease.

Small intestinal disease usually involves the jejunum, where direct visualization can be challenging. Intestinal ulcers due to TB are classically described as circumferential and surrounded by inflamed mucosa. Capsule endoscopy should be cautiously utilized, as the presence of strictures may lead to capsule retention. After endoscopic balloon dilatation of strictures, obtaining biopsies from upstream segments can increase the diagnostic yield.

Fine-needle aspiration cytology or core biopsy of the mediastinal, celiac or peripancreatic lymph nodes may be acquired via endoscopic ultrasound.

Diagnostic laparoscopy may be useful in suspected cases of abdominal TB when the above investigations are inconclusive or when a peritoneal location is strongly suspected. During the procedure, a biopsy from the peritoneum or lymph nodes can be taken under laparoscopic vision. However, there may be a need to convert to open surgery when dense adhesions are present.

Figure 10: Characteristic colonoscopy findings of intestinal TB. (A) Transverse ulcerations. (B) Ulcer scars with pseudo polyps. (C) A "fish-mouth" ileocecal valve.



9.4.5 Histopathology

The hallmark for the histological diagnosis of TB is caseative type necrosis. Granulomas and clumps of granular/caseative type necrosis are also highly indicative of TB on FNAC. Numerous, large, coalescing granulomas with central necrosis may be seen in the peritoneum and in ileocolic, mesenteric and bowel wall lymph nodes. Langhans giant cells, lymphocytic cuffs and peri granuloma fibrosis may also be present. According to Dasgupta et al., granulomatous inflammation in the mesenteric vasculature was associated with bowel wall perforation.

It is not always helpful to stain tissue and cytology samples for acid-fast bacilli, as the literature reports a range of positive results from 6-8% to 53.4%. Even in the absence of bacteriological evidence, caseating granulomatous inflammation is thought to be adequate to support a diagnosis of intestinal TB.

As mentioned earlier, Crohn's disease is the primary differential diagnosis for intestinal TB. Large, confluent granulomas with caseative type necrosis that are primarily found in the submucosa and subserosa, granulomatous lymphadenitis without inflammation of the bowel wall and the absence of deep fissures are the histopathological characteristics of TB that are most helpful when compared to Crohn's disease. Furthermore, granulomas are far more common in TB than in Crohn's disease. It is important to note that resection specimens frequently include the majority of these distinguishing features, whereas the results of endoscopic biopsies maybe non-specific and non-diagnostic.

Cultures are the Gold Standard Test for diagnosing Abdominal TB as well. peritoneal fluid aspirates (paracentesis)or gastrointestinal biopsies shows higher sensitivity for both Gene Xpert 95.7% and TB culture 35.0%. Samples should be at least 1 ml in volume and collected aseptically. It must be sent in regular saline rather than Formal saline.

9.4.6 Ascitic Fluid Analysis

The ascitic fluid is typically an exudate with a serum-ascites albumin gradient (SAAG) of less than 11 g/L and a protein concentration of more than 30 g/L. A leukocyte count of 150 to 4000 cells/mL, predominantly lymphocytic, is one indicator of abdominal TB or disseminated TB with abdominal involvement. Ascites to blood glucose ratios are typically less than 0.96. An ADA of more than 39 IU/L is suggestive of abdominal TB. While Xpert MTB/RIF Ultra for peritoneal TB utilizing peritoneal fluid has a pooled sensitivity of 59%, AFB smear and culture of ascitic fluid both have disappointingly poor yields (AFB positive in 3%, culture positive only in 20% of patients). Xpert MTB/RIF Ultra for peritoneal TB using peritoneal fluid has a pooled sensitivity of 59% and a pooled specificity of 98%.

Table 10: Comparison of Crohn's disease and Ileocecal TB

	Crohn Disease	**Iliocecal TB**
Clinical features	Mainly diarrhea, haematochezia, perianal disease, extra intestinal manifestation (arthralgia, aphthous ulcers dermatologic and ocular manifestation)	Mainly fever, night sweats, lung involvement, ascites
Radiology Finding	CT findings involvement of left colonic segment. Long segment involvement, presence of skip lesions, presence of	Involvement of ileocecal area, shorter length of

	comb sign. Asymmetric wall thickening, segmental intestinal involvement, comb sign, mesenteric fibro fatty proliferation	involvement, presence of lymph nodes larger than 1 cm
Endoscopy Finding	Left colonic involvement, presence of longitudinal ulcers, aphthous ulcers, cobblestone appearance, skip lesions, anorectal lesions, luminal stricture, mucosal bridge	Presence of transverse ulcers, patulous ileocaecal valve are more common. Fewer than 4 segment involvement. Pseudopolyps, presence of Ileocolic valve and cecal involvement
Histopathology	Small granuloma (micro granuloma) Discreate ill-defined sparse lesions, architectural distortion distant to granulomatous inflammation. focal enhanced colitis	TB granuloma (large >200 mm) confluent dense (>5-10/hpf) Located in submucosa, characterized by central caceation (diagnostic and exclusive) sub mucosal granulomas, ulcer lined by a band of epithelioid histiocytes, disproportionate sub mucosal inflammation

9.5.1 Place of Surgery in abdominal TB Treatment

Intestinal obstruction is the most frequent presenting symptom that may require surgery. Subacute intestinal obstruction in intestinal TB may be brought on by a thickened constricted caecum. Multiple strictures are present in some cases. The symptoms are frequently responsive to antituberculous medication.

The cicatrization process during healing however, can cause obstructive symptoms to worsen while receiving treatment. It may be wise to manage conservatively until the investigation findings are available to confirm the diagnosis of intestinal TB when the history, imaging, and endoscopic features are compatible with low-grade intestinal obstruction. If medical treatment is not effective, there may be a need for stricturoplasty, adhesiolysis or bowel resection. If the ileal stricture is short, colonoscopy-assisted balloon dilatation is a viable option Fistulectomy, bowel resection or drainage may be required. These cases should be discussed in a multi-disciplinary setting. Place of adjunctive corticosteroids is debateful. However, some studies

suggest a trend towards a reduction in pain, obstruction and need for laparotomy in those prescribed adjunctive corticosteroids.

9.6 Follow-up

It might be challenging to objectively evaluate a patient's response to therapy. The remission of fever and constitutional symptoms, an improvement in biomarkers like ESR and CRP, and/or a combination of these are regarded as surrogates for therapeutic success. Anti-TB medication typically results in an improvement in symptoms within a few weeks, and the majority of patients recover completely within two months.

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Chapter 10: OCCULAR TUBERCULOSIS

10.1 Introduction

TB is a chronic granulomatous infection primarily affecting the lung, but other organs including the eye may get involved. The term "ocular TB" describes an infection by the *M. tuberculosis* species that can affect any part of the eye (intraocular, superficial, or surrounding the eye), with or without systemic involvement. Delay in diagnosis and treatment can result in chronic inflammation and loss of vision. Improving access to a diagnosis is therefore a high priority.

10.2 Pathogenic Mechanism of Ocular Tuberculosis

Ocular tuberculosis (OTB) encompasses all forms of intra- and extra-ocular inflammation associated with MTB infection. However, the organism is rarely found in ocular fluid samples of diseased eyes, rendering the pathological mechanisms of the disease unclear. This confounds clinical decision-making in diagnosis and treatment of OTB.

Broadly there appear to be two fundamental mechanisms that may underlie the development of TB-associated ocular inflammation:

a. Inflammatory response to live/ replicating *MTB* in the eye
b. Immune mediated ocular inflammation induced by non-viable *MTB* or its components in the eye.

This distinction is significant as in direct *MTB*-driven mechanisms, diagnosis and treatment would be aimed at detection of *MTB*-infection and its elimination; while indirect mechanisms would primarily require anti-inflammatory therapy with adjunctive anti-TB therapy. Often both responses **co-exist** where one mechanism can predominate.

10.3 Prevalence of the OTB

The lack of the diagnostic criteria coupled with difficulty in establishing tissue or microbiological diagnosis has led to be believed that OTB was rare. However, recent reports have shown that TB may indeed be a common cause of uveitis.

A significant proportion of infective uveitis is caused by TB. OTB can cause moderate to severe visual impairment in up to 40% of affected eyes.

Table 11: Country specific information on ocular TB in some Asian countries

Country	Prevalence of presumed ocular TB
India	0.4-9.8%
China	4.0%
Japan	7.0%
Thailand	2.2%
Philippines	6.8%

(Source: American Academy of Ophthalmology, 2024)

10.4 Clinical features of Ocular TB

The clinical lesions of TB may affect any ocular tissue including sclera, lacrimal sac, uvea, retinal vessels, the optic nerve head and orbit. The commonest presentation is **Uveitis** and they may present either as anterior, intermediate, posterior or pan uveitis in one eye or bilaterally (usually asymmetric) presenting as acute, subacute, or chronic uveitis.

The common presenting ocular symptoms are pain, photophobia, red eye, blurring of vision and floaters. Apart from the direct causes affecting the eye, vision may also can get affected in patients due to TBM and toxic drug reactions to the ATT.

10.4.1 Anterior Uveitis

Tuberculous uveitis predominantly involving the anterior chamber with absence of posterior signs is termed anterior uveitis.

1. The most characteristic feature is the presence of multiple mutton fat, yellowish white granulomatous keratitic precipitates. The iris may be thickened and have multiple nodules near the pupillary border and/or iris root.

2. Non granulomatous uveitis - should raise suspicion when bilateral, recurrent or when associated with broad based posterior synechiae.

3. Angle granuloma with minimal anterior chamber reaction

10.4.2 Intermediate uveitis

Primary Vitritis in the absence of retino-choroidal involvement is considered as Intermediate Uveitis. The snow ball opacities are seen as a string of pearls inferiorly in the vitreous cavity with or without vitreous haze. Isolated tuberculous intermediate uveitis is uncommon.

10.4.3 Posterior uveitis

Posterior segment involvement is one of the commonest – vision threatening - presentation of OTB. Choroidal tubercle, Retinal vasculitis and serpiginous choroiditis are the most typical presentations of posterior uveitis caused by TB.

Choroidal Tubercle

Choroidal tubercles are the most characteristic finding of OTB. Nearly 25 to 30 percent patients of disseminated/miliary TB and tubercular meningitis may show choroidal tubercle. The tubercles may be unilateral or bilateral. Retinal detachment can occur overlying choroidal tubercles. These lesions usually heal over several weeks with or without treatment leaving behind atrophic, variably pigmented scars. In HIV patients, choroidal tubercles are asymptomatic and picked up only on routine examination. Solitary tuberculoma mimicking a tumor occurs less commonly.

Retinal Vasculitis

Retinal vasculitis primarily affects the retinal veins but rarely the arterioles. It usually affects small or large segments of retinal veins, appearing as fluffy grayish white perivascular infiltrates with associated superficial hemorrhages. Macula may also be affected with macular oedema and hard exudates. Over a period of several weeks the vasculitis heals leaving behind residual hemorrhage and exudates. The retinal vasculitis can cause extensive ischemia of the retina leading to development of retinal neovascularization, which may result in either preretinal/subhyaloid hemorrhages or frank vitreous hemorrhages. This can lead to sudden loss of vision. Untreated retinal neovascularization can lead to tractional retinal detachment.

Serpiginous like choroiditis

Initially they appear as single or multifocal placoid lesions in the posterior pole along the retinal blood vessels. Later they become contiguous with an advancing edge similar to Immune mediated serpiginous choroiditis.

Large Subretinal Abscess/Granuloma

Usually occur in one or both eyes in patients with disseminated TB and these lesions represent rapidly multiplying tubercular bacilli. Vascular malformations and hemorrhage within granuloma are characteristic features. They are often accompanied by exudative retinal detachment. Rapidly progressive disease may cause endophthalmitis and panophthalmitis.

10.4.4 Optic Neuropathy

Is caused by either hematogenous spread from lung or other primary focus or spread from adjacent choroid. They can present with various manifestations such as papillitis, retrobulbar neuritis, neuroretinitis, or opticochiasmatic arachnoiditis.

10.4.5 Tuberculous scleritis

Infectious TB scleritis is suspected in the presence of purulent exudates, scleral ulcers, scleral abscesses, and scleritis associated with hypopyon. Immune-mediated TB scleritis in patients with active systemic TB is associated with phlyctenular keratitis, phlyctenular keratoconjunctivitis, and episcleritis.

10.4.6 Orbital TB

Orbital and periorbital disease is usually acquired by haematogenous or lymphatic spread and more rarely by direct spread from skin inoculation or the paranasal sinuses.

Presentations include:

- Eyelid or periorbital cutaneous TB
- Lacrimal gland and sac involvement
- Bone involvement
- Inflammatory masses within the orbit

Patients may present with pain, proptosis, and diplopia or reduced vision secondary to compressive optic neuropathy. Orbital biopsy may be required to exclude malignancy.

10.4.7 Immune recovery uveitis

- Can occur among patients with concurrent HIV and TB infection during antiretroviral therapy

- Has also been reported among patients with HIV and concurrent TB, cytomegalovirus retinitis, and varicella zoster ocular infection.

10.5 Diagnosis of OTB

Diagnosis of the OTB is difficult, for obvious reasons, the intraocular fluid for culture is scanty, organisms are too slow to grow in cultures and a negative culture does not rule out the diagnosis of OTB. Similar presentation of ocular involvement can be seen in other medical conditions such as sarcoidosis, toxoplasma, syphilis, collagen vascular diseases etc. hence appropriate investigation needs to be carried out to exclude suspected causes.

10.5.1 Systemic Investigations

- **TST**: Mantoux reaction is important in tuberculous uveitis as cutaneous hypersensitivity is shown to be related to ocular hypersensitivity (since SL is an endemic area we take >10 mm as positive, but in the immune suppressed people 5-10 mm may be significant). A positive Mantoux should be supported with typical clinical features of ocular TB in an endemic country like ours.

- **IGRA:** Single-visit blood test that quantifies IFN-γ response of T cells after in vitro stimulation of patient lymphocytes by MTB antigen. This test is more specific, not affected by prior BCG vaccination and atypical mycobacteria. But it is not superior to TST in sensitivity, high cost, technical difficulty; does not distinguish between latent and active disease.

- **Chest Radiography:** Evidence of healed or active tubercular lesion on CXR is supportive of diagnosis, although OTB can occur in the absence of lung disease. CT of the chest (High Resolution) is indicated in patients with high degree of suspicion even when the CXR is normal. In the presence of such lesion Mantoux of 5-10 mm is significant.

- Evidence of EPTB diagnosed by demonstration of tubercular granuloma/culture of *M. tuberculosis.*

- **Fluorescein angiography:** Used in the evaluation of retinal vascular leakage and active choroidal lesions.
- **Ultrasonography:** Reveals moderate to low internal reflectivity of large tuberculomas

It is also important to exclude other infective/non infective uveitis.

Differential diagnosis

- **Granulomatous uveitis**
  - Sarcoidosis
  - Syphilis
  - Herpes simplex
  - Varicella zoster
  - Leprosy
  - Vogt-Koyanagi-Harada disease
  - Sympathetic ophthalmia
- **Choroidal granulomas or Chorioretinitis**
  - Syphilis
  - Sarcoidosis
  - Fungal lesions
  - Cryptococcus
  - Serpiginous
  - Toxoplasmosis

10.5.2 Ocular investigations

Clinical practice points

1. Tests on all patients with uveitis and positive IGRA: U&E, eGFR, LFT, FBC, CXR. Syphilis serology, HIV, Hepatitis B and C screen, sputum samples for AFB and culture if coughing.
2. Tests depending on ocular phenotype, systematic enquiry and clinical findings elsewhere
3. HLA-B27 & A29, serum ACE, CRP, ESR, ANCA, ANA. Toxoplasmosis serology, Lyme (Borrelia) serology

- Positive **PCR** from aqueous, vitreous humor, subretinal fluid, or chorioretinal biopsy

- Sample collection: Anterior chamber/vitreous tap using a 30G needle attached to a 2 -ml syringe to collect 50–100 µl of aqueous. Specimen to be sent to the laboratory immediately.

- Demonstration of **AFB** (Ziehl Neelsen) from the ocular fluid is useful only in endophthalmitis

- As **Culture** of *M. Tuberculosis* from the ocular fluid takes time, it is of limited value.

10.6 Treatment of OTB

10.6.1 Medical Management

Anti tubercular drugs used for OTB are same as PTB. The role of concomitant use of corticosteroid therapy is essential. Systemic corticosteroids should be started as early as possible and continued for 4 to 6 weeks, along with multidrug ATT as it is helpful in limiting damage to the ocular tissues from delayed type hypersensitivity.

Note:

- A **positive therapeutic response** to anti-tuberculous therapy over a period of 4-6 weeks is highly suggestive of a possible tubercular aetiology. Since the ocular fluids are not readily available for retesting, clinical ophthalmic examination is the mainstay in assessing therapeutic response. If lesions resolve within 2 months, ATT for 6 months may be enough. Poor response necessitates second line of ATT or re-evaluation.

- Any **flare up** of uveitis following completion of ATT can be treated with steroids alone or with immunosuppressants if needed.

- **PR** (worsening of the ocular lesions) should be looked for during initiation of ATT and should be treated appropriately.

10.6.2 Surgical Management:

- Laser -Retinal photocoagulation is indicated in the presence of significant ischemia due to retinal vasculitis Pars plana vitrectomy (diagnostic and therapeutic vitrectomy) is done for challenging cases with dense vitritis or tractional retinal detachment.

Clinical practice points

1. Visual acuity alone is insufficient as a measure of outcome from treatment.
2. Improvement in fundus imaging can be used as an outcome measure when chorioretinitis and/or retinal vasculitis is affecting the peripheral retina.
3. The SUN criteria are useful standardized methods of assessing uveitis activity.
4. A reduction in steroid dose (typically below 7.5 mg per day) can be used as an outcome measure.

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Chapter 11- EPTB PLEURAL EFFUSION

11.1 Introduction

Tuberculous pleural effusions (TBPE) are second only to tuberculous lymphadenopathy in terms of incidence of EPTB worldwide. The HIV/ AIDS pandemic has resulted in doubling of the incidence of extra-pulmonary TB and the increasing recognition of TBPE.

11.2 Epidemiology

The frequency of pleural involvement has been variably reported (4% in the United States to 23% in Spain). The incidence of TBPE in HIV/ AIDS patients has been variably reported from 15 to 90%.

In Sri Lanka too, lymphadenopathy is the commonest form of EPTB accounting for 35 % while TBPE accounts for 20%. The number of extra-pulmonary cases of TB reported over the years has been increasing in Sri Lanka. According to the 2021 TB annual report from NPTCCD, TBPE accounts for 330 cases (18%), out of 1833 cases of EPTB.

11.3 Pathogenesis

TBPE was commonly thought to be an effusion as a result of a pure delayed hypersensitivity reaction. However, now it is believed to be the consequence of direct infection of the pleural space followed by a cascade of events including an immunological response.[1] TBPE can manifest as primary or reactivated disease. Rupture of a subpleural caseous focus in the lung and the consequent release of Mycobacterial antigens into the pleural space is considered the initiating event in the pathogenesis of Primary TBPE.

The early response to pleural injury by MTB is characterized by a rapid influx of polymorphonuclear leukocytes, particularly neutrophils. This is followed by macrophage influx, and thereafter a prolonged lymphocyte-driven immune reaction.[2] This results in an interaction with predominantly $CD4^+$ T–lymphocyte, mediated delayed hypersensitivity reaction. This may occur during primary or reactivation of TB and may or may not involve viable bacilli entering the pleural space.

The $CD4^+$ T-lymphocytes are of the T-helper type 1 (Th_1) cells resulting in an (INF-γ and interleukin-12 (IL-12) driven cytokine profile. INF-γ is essential for macrophage activation, killing and containment of mycobacteria. Intercellular adhesion molecule-1 (ICAM-1) is also

over expressed resulting in increased capillary permeability and accumulation of fluid in the pleural space. The protein rich exudates causing blockage and impaired drainage of lymphatics would also contribute to this. Reactivation of disease is frequently associated with parenchymal diseases and results from entry and active replication of mycobacteria in the pleural space.

11.4 Clinical features

Although TB is considered a chronic illness, TB pleuritis most commonly manifests as an acute illness. One third of patients are symptomatic for < 1 week and the remaining two thirds are symptomatic for < 1 month. Pleuritic chest pain (75%) and non-productive cough (70%) are the commonest symptoms. Pain usually precedes the cough. Most patients are febrile but a normal temperature does not rule out the diagnosis. TBPE though considered a disease of the young (mean age 28 years), can present in the elderly and in these instances is mostly due to disease reactivation.

HIV positive patients with TBPE tend to be older, have a higher incidence of fever, dyspnea, night sweats, hepato-splenomegaly and lymphadenopathy. They are more likely to have a pleural fluid smear and culture positive for *M. tuberculosis*, a positive pleural biopsy result and /or a negative tuberculin test. TBPE are typically unilateral and small to moderate in size occupying less than 2/3 of hemithorax. Chronic TB empyema, which represents active infection of the pleural space, can result in the development of a bronchopleural fistula (BPF) or empyema necessitans (empyema fluid breaks out through the chest wall).

11.5 Diagnosis

The definitive diagnosis of TBPE depends on the demonstration of *M. tuberculosis* in sputum, pleural fluid and/ or culture of pleural biopsy specimens. Classical granulomas on a pleural biopsy specimen, a positive tuberculin test, elevated ADA, positive NAAT and INF γ levels in pleural fluid are supportive of the diagnosis.

11.5.1 Sputum examination

Pulmonary involvement is more common than previously believed and induced sputum for TB culture, which is grossly under-utilized, can be diagnostic in approximately 50% of TBPE. Hence, even in the absence of radiological evidence of parenchymal involvement, 12% will

have a positive smear result in an induced sample of sputum. Whenever, there is a pleural effusion, look for coexisting parenchymal changes suggestive of pulmonary TB.

Recommendation- Sputum induction with direct smear and culture should be perused in all patients with suspected TBPE.

11.5.2 Tuberculin Skin Testing

A positive TST (Mantoux) is supportive of TBPE in areas of low prevalence. A negative result occurs in 1/3 of patients with TBPE. A negative result can occur in the following situations;

1) Anergy secondary to immuno- suppression or malnutrition.
2) HIV positivity.
3) Sequestration of purified protein derived T-lymphocytes in pleural space.

(Refer chapter 03 for more details).

Recommendation- A TST should be part of the diagnostic work up of TBPE.
A positive TST is supportive of a diagnosis of TBPE but should be interpreted along with other evidence of pleural fluid examination. A negative test does not rule out TBPE.

11.5.3 Imaging

Chest radiography usually reveals a small to moderate unilateral pleural effusion. Parenchymal involvement occurs in around 20%. Contrast enhanced CT scans can increase this diagnostic sensitivity by demonstrating lung parenchymal involvement (86%) and lymphadenopathy. In analyzing chest radiographs and CT scans among patients with TBPE, bilateral effusions were noted in 18%, more commonly over age 65 years. Lung consolidation was noted in 50%. US are useful in demonstrating fibrin bands, septations, encysted fluid, pleural thickening and occasionally pleural nodules. USS is also useful in performing guided aspirations, intercostals (IC) tube placement and guided biopsy.

Recommendation: Chest radiography usually reveals a small to moderate unilateral pleural effusion. Parenchymal involvement occurs in around 20%. Contrast enhanced CT scans can increase this diagnostic sensitivity by demonstrating lung parenchymal involvement (86%) and lymphadenopathy. In analyzing chest radiographs and CT scans among patients with TBPE, bilateral effusions were noted in 18%, more commonly over age 65 years. Lung consolidation

was noted in 50%. US scans are useful in demonstrating fibrin bands, septations, encysted fluid, pleural thickening and occasionally pleural nodules. US scans is also useful in performing guided aspirations, IC tube placement and guided biopsy.

11.5.4 Pleural fluid analysis

A TBPE is typically clear and straw coloured, but can be turbid or serosanguinous and never grossly bloody. It is important to document macroscopic appearance of the fluid. It is always an exudate. PH is usually around 7.30 -7.40. In 20% it can be < 7.30. Glucose is > 60 mg /dl in 80 – 85% of cases though in 15% it can be < 30 mg /dl. Specimens for cytology must be sent in an EDTA bottle and a differential cell count requested. Older literature suggests that a pleural fluid mesothelial cell count of > 5% virtually excludes TBPE. This is because uniform inflammation of pleural surface virtually prevents exfoliation of mesothelial cells into pleural cavity. However, there have been case reports of HIV positive patients with higher mesothelial cell counts in pleural fluid.

A pleural fluid eosinophil count of > 10 % virtually excludes TBPE unless there is a pneumothorax or repeated thoracenteses has been performed. In the first two weeks of illness cells may be predominantly neutrophillic, if serial thoracenteses is performed this shows a shift towards predominantly a lymphocytic fluid. A minority of patients progress through the lymphocytic phase of the disease to a second neutrophil predominant phase, indicating the presence of complications of chronic pleural infection such as a loculated effusion or frank empyema. [3] Not surprisingly, these patients have a higher rate of culture positivity for MTB.

Recommendation: All patients with undiagnosed pleural effusions will need a diagnostic pleural tap. Utilization of ultra-sound scans for guided aspiration or marking of site for aspiration will result in higher rate of successful pleural aspiration. A lymphocytic exudative effusion is usually seen; however, neutrophilic predominance will not exclude the diagnosis.

11.5.5 Microbiology

Direct examination of pleural fluid by Zeihil-Neelson staining detects AFB in < 10 % of cases. In suspected TB empyema yields are higher. In HIV positive patients yield is > 20 %. Culture for mycobacteria is conventionally positive in less than 40%.

Bedside inoculation of mycobacteria into culture media, use of liquid for culture has shown an increased diagnostic yield. With this advent of improved culture techniques, it is now possible

to culture *M. tuberculosis* from both pleural fluid and pleural tissue in as many as 70% of cases.[1] Pleural fluid culture yielded a diagnosis is 16% and pleural biopsy culture yielded 54%.[4]

Recommendation: All patients should have pleural fluid sent for TB culture.

11.5.6 Adenosine Deaminase (ADA)

ADA is the enzyme that catalyzes the conversion of adenosine to inosine. It is a predominant T lymphocyte enzyme and its activity is increased in conditions which cellular immunity is stimulated. There are two molecular forms of ADA. ADA1 and ADA 2. ADA1 is found in all cells but greatest activity is in lymphocytes and monocytes. ADA 2 is found in monocytes and macrophages. The majority of ADA found in TBPE is of ADA 2, ADA 1 is found in other pleural effusions also. ADA 1/ ADA 2 ratio of < 0.42 will only slightly increase the sensitivity and specificity of ADA in the diagnosis of TBPE and is not needed in the vast majority of the cases as cost of test is higher.

An ADA level of > 70 IU / L is highly suggestive of TBPE and a level < 40 IU /L virtually excludes the diagnosis. The specificity is increased when the lymphocyte / neurtrophil ratio of > 0.75 and an ADA level of > 50 IU / L is considered.

The ratio between ADA and lactate dehydrogenase (LDH) of less than 16 supports a diagnosis of TBPE, while a ratio of more than 60, favors a diagnosis of bacterial empyema.

ADA measurement is a rapid, minimally invasive, relatively inexpensive test which is gaining popularity because of sensitivity of 95 % and specificity of 90 % respectively and could replace pleural biopsy in high TB prevalence regions.

ADA levels in TBPE in HIV/ AIDS, renal transplant patients are comparable to those of immuno – competent people.

Other reported conditions in which pleural fluid ADA is increased include rheumatoid arthritis, pleural empyema (pleural fluid is neutrophilic in these two conditions), mycoplasma, clamydia pneumonia, histoplamosis, brucellosis, bronchoalveolar carcinoma. Most of these conditions can be differentiated on the basis of clinical history and other investigations.

The specificity for discriminating TB from malignant effusions, an important differential diagnosis in the elderly, remained high (95%) but was disappointingly low for parapneumonic effusions.

Recommendations: ADA measurement is a rapid, minimally invasive, relatively inexpensive test with a sensitivity of 95% and specificity of 90% respectively and could replace pleural biopsy in high TB prevalent regions. This should be performed in all clinically suspected TBPE with pleural fluid lymphocytosis whenever facilities available.

11.5.7 Nucleic acid amplification tests (NAATs)

Several commercial and in-house assays exist for the amplification and detection of *M. tuberculosis* nucleic acids from specimens such as sputum. These tests have also been used with specimens such as pleural fluids.

In a meta-analysis of 40 studies of NAATs for pleural TB, Pai et al. reported that commercial nucleic NAATs have a potential role in confirming TB pleuritis because of a higher specificity of 98% (95% CI 96–98).

The sensitivity of the MTB Xpert/RIF Ultra assay in diagnosing TBPE was 16.6%, specificity was 100% and diagnostic accuracy was 52.5%. The positive and negative predictive values were 100% and 47.5% respectively.[5]

The presence of inhibitory substances in pleural fluid, the small amount of mycobacteria in pleural effusion or technical aspect of nucleic acid extraction may play a role in NAAT being low in sensitivity.

Recommendations: The evidence is consistent that NAATs have modest sensitivity but excellent specificity for PTB and EPTB. At present, no commercial kit has been approved for the diagnosis of EPTB, and NAATs cannot be used in isolation to rule in or rule out pleural TB. Disadvantages include the sophisticated technology involved, cost, false positives due to contamination. The evidence for the use of PCR in the diagnosis of TBPE is not as favorable for ADA.

11.5.8 T-cell response to specific antigens / Interferon Gamma testing

IGRAs, designed to detect latent TB infection and currently cannot be recommended for diagnosis of TBPE in isolation, although this may help in conjunction with other biomarkers in differentiating TBPE from malignancies.

11.5.9 Neopterin

Neopterine is a marker of T-cell activation, is secreted by activated macrophages. Levels in pleural fluid have been found to be higher than in patients with TB than patients with malignancy or other conditions. However very high levels have been reported in ureamic pleural effusions rising doubts about it's specificity for TB.

In one study that used histopathology as the reference standard for TB, the sensitivity and specificity for neopterin were 44 % and 85 % respectively. This test is not available in Sri Lanka.

11.5.10 Lysozyme

Lysozyme is present in epithelial cells of granulomas, macrophages and activated granulocytes. A recent meta-analysis (2022) concluded that there is low-quality evidence of good diagnostic accuracy for pleural lysozyme level and pleural: serum lysozyme ratio in differentiating TBPE from malignant and para-pneumonic effusions.[5] This test is not available in Sri Lanka.

11.5.11 B-cell response (antibody detection)

Serologic tests using antibodies against mycobacterial protein [IgA against MPT-64 and MT-10.3 (Rv3019c)] and glycolipids show some potential for the diagnosis of pleural TB because of their high specificity, but are limited by very poor sensitivity.

11.5.12 Other newer pleural fluid assays

a) MTB cell-free DNA (MTB cfDNA) in the pleural fluid

The MTB cfDNA assay produced a sensitivity of 79.5% for TBPE, which was superior to sensitivities of GeneXpert (38.5%) and culture (27.1%).[6]

b) Pleural fluid Leptin assay

Leptin, a 16-kDa product of the obese (ob) gene, may be involved in cross-regulation between nutritional status and the immune response in TB.[7]

Serum leptin levels have been shown to be reduced in patients with active pulmonary TB and cancer.

One study evaluated total leptin pleural fluid levels and leptin pleural fluid/serum ratio in 17 patients with pleural TB, and parapneumonic and malignant effusions.

There is no evidence that leptin performs better than pleural fluid ADA.

c) Pleural fluid IL-27 levels

This carries a sensitivity of 92.7% and specificity of 98.8%.[8]

d) Loop-mediated isothermal amplification (LAM)

Detection of LAM (a TB antigen) using ELISA, phage-based assays and rapid culture systems.

To date, none of these have been adequately evaluated for TB pleuritis

11.5.13 Pleural biopsy

Abram's pleural biopsy is termed "blind" or "closed" biopsy because pleural surface is not directly visualized.

In patients with TBPE biopsy reveals granuloma in 50 -97 % of patients, culture from biopsy material would reveal mycobacteria in 39 – 80 % patients.

When both methods are combined the diagnostic yield is 60 – 95 %. In present days closed biopsy is largely replaced by thoracoscopic pleural biopsy which carries a better diagnostic yield.

11.5.14 Thoracoscopy and guided pleural biopsy

Thoracoscopy has been used extensively for the diagnosis of pleural TB and malignancy. Thoracoscopy may show yellow-white tubercles on parietal pleura which are mostly concentrated in the costovertebral angles. It also allows targeted biopsy of suspicious lesions, under direct visualization.

In a recent study thoracoscopic pleural biopsy was found to produce a histological diagnosis in 37/39 (95%) of microbiologically confirmed TBPE.[4] However, the procedure required expertise and expensive equipment to perform. The advent of Video-assisted Thoracoscopic Surgeries (VATs) has made available further evaluation of pleural disease.

Recommendation- All patients with suspected TBPE (especially if cytology is lymphocyte predominant) should have a pleural biopsy with histology and culture of pleural tissue. Pleural tissue specimens for culture should be sent in normal saline. In patients with undiagnosed

pleural effusion in whom Abrahams Needle guided pleural biopsy has not been of help, thoracoscopic pleural biopsy is recommended.

11.6 Treatment

The natural history of TBPE is characterized by spontaneous resolution in 4 – 16 weeks; though some residual pleural thickening may remain especially if the effusion is loculated, lower pleural fluid glucose and higher pleural fluid LDH.

Pulmonary TB can develop in 43 – 65 % of patients over the next several years if TBPE is left untreated.

Uncommonly, untreated effusions proceed directly to a tuberculous empyema.

The treatment of tuberculous pleuritis has three goals:

(i) to prevent the subsequent development of active TB

(ii) to relieve the symptoms of the patient

(iii) to prevent the development of a fibrothorax

Treatment is INH, Rifampicin, Ethambutol and Pyrazinamide for 2 months (intensive phase) with Rifampicin, INH for 4 (continuation phase) in fixed dose combinations (FDC).

HIV-TBPE coinfection

Patients with HIV/ AIDS with TBPE are treated similarly. Clinicians must be aware of drug interactions with anti-TB drugs in patients on highly active antiretroviral therapy (HAART) and the Immune Reconstitution Syndrome (Refer chapter 12).

HIV-positive people who are not yet on ART at the time of TB diagnosis and who have a CD4 count <50 cells/μL should have their ART initiated within 2 weeks of TB therapy.

In all other cases, a delay of 6–8 weeks before ART initiation is acceptable.

Rate of response to ATT

The time to resolution of symptoms such as fever varies from 2 weeks to 2 months.

Radiographic evidence of resolution of the effusion may take 12 weeks or longer, depending on the size of the effusion.

PRs and IRIS: Up to 26% of patients with TBPE demonstrate a paradoxical worsening in symptoms and radiographic findings soon after treatment initiation.

This phenomenon can occur as part of the immune reconstitution inflammatory syndrome (IRIS) in HIV-positive individuals.

However, it is often seen in HIV-negative patients; especially young, previously healthy males with TB involving the subpleural lymphatics on CT chest.

ATT should be continued despite worsening of the TBPE in case of IRIS.

11.6.1 Corticosteroids

Randomized studies have investigated the possible adjunctive role of oral corticosteroids in TBPE. Doses of 0.75 – 1 mg / kg / day were used in periods ranging from 4 – 12 weeks. Corticosteroids may reduce the time to resolution of pleural effusion.

Though early resolution of fever, chest pain and dyspnea were observed there was no difference in the development of residual pleural thickening or adhesions on follow up.

Residual lung function was similar to the group that did not receive steroids.

Recommendations- There is insufficient evidence to support the use of steroids in TBPE.

11.6.2 Therapeutic needle aspiration

Data on this topic is sparse. In large effusions, therapeutic needle aspiration relieves dyspnoea rapidly, and is associated with long-term reduction in residual pleural thickening and minor improvements in lung functions. In smaller effusions; there is no indication for performing a therapeutic needle aspiration.

11.6.3 Surgical procedures

Patients who are symptomatic with large pleural effusions will require IC drainage.

In TBPE complicated by septations, multiple loculi and pleural thickening, intra-pleural instillations of streptokinase (250 ,000 IU in 100 ml normal saline via IC tube after an initial test dose), tube is left clamped for 4 hours. Patient is mobilized to facilitate uniform distribution of streptokinase. Instillations are given twice daily up to five days.

Tissue plasminogen activator (tPA) is an accepted alternative fibrinolytic agent.

VATs Decortication surgery should be delayed until 4-6 months of anti-TB chemotherapy; as pleural peel has to mature enough for surgical stripping.

11.7 Complications of TBPE

11.7.1 Bronchopleural Fistula (BPF)

This complication is uncommon today because of the availability of anti-TB chemotherapy. It is a complication in patients with reactivation of TB with chronically diseased underlying lung. When such patients develop BPF their sputum production increases and is at risk of invasion of pleural space by bacteria resulting in septicemia. Also infected material enters the tracheobronchial tree from infected pleural space resulting in a fulminant pneumonia

The diagnosis is suggested by the presence of an air-fluid level in the pleural space, particularly if the level fluctuates with serial chest radiographs. The fistula can be confirmed by injection of methylene blue or a radiopaque dye into the pleural space.

Treatment is with standard regimens of anti –TB chemotherapy and IC tube drainage. A surgical procedure should not be attempted until the patient is given 90 -120 days of anti –TB chemotherapy or patients sputum tests are negative for AFB. However, depending on the clinical progression, early surgical interventions may be required. Definitive surgical treatment consists of simple suturing, partial lung resection with or without decortication. Surgery carries a high morbidity and mortality.

11.7.2 Pseudo chylous effusions

TBPE can present as pseudo chylous or cholesterol effusions. Pleural fluid cholesterol concentration will be more than 200 mg/d. Pleural fluid triglyceride concentration is less than 110 mg/dL.

11.7.3 TB empyema

It is a less common complication of PTB. It is usually the result of the rupture of a cavity, with spillage of a large number of organisms into the pleural space. Frequently the underlying pleurae are heavily calcified.

Other mechanisms of TB empyema include; direct spread of infection from a ruptured thoracic lymph node/ subdiaphragmatic focus or hematogenous spread from a distant focus or following pneumonectomy.

TB empyema has three stages of evolution have been described:

1. Exudative phase (clear, viscous and often sterile effusion)
2. Fibrinopurulent phase (thick, infected, purulent fluid)
3. Organizing phase (granulation tissue formation with lung encasement)[9]

The patient has a sub-acute or chronic illness characterized by fatigue, low-grade fever and weight loss. Patients with TB empyema present with chest pain, breathlessness, cough with expectoration, fever, and septicemia. Anaemia and hypoproteinaemia are often present. Physical examination may reveal finger clubbing, clinical findings suggestive of effusion and IC tenderness. Occasionally, TB empyema may present as a chest wall mass or draining sinus tract (TB empyema necessitans). Radiographically, there may be obvious pleural effusion, but frequently the chest radiograph only shows pleural thickening. The chest CT demonstrates a thick, calcified pleural rind and rib thickening surrounding loculated pleural fluid.

Thoracentesis yields thick pus on which AFB smear is positive. This process may create a BPF with evident air in the pleural space where a chest radiograph will show a hydropneumothorax with an air-fluid level. Hydro-pneumothorax, upon drainage develops into a chronic pneumothorax with a persistent air leak that resists expansion and closure even upon multiple drainage and low-pressure suction.[10]

The pleural fluid is purulent and thick and contains large numbers of lymphocytes. Acid-fast smears and mycobacterial cultures are often positive. Surgical drainage is usually required as an adjunct to chemotherapy.

Tuberculous empyema may result in severe pleural fibrosis and restrictive lung disease. Removal of the thickened visceral pleura (decortication) is occasionally necessary to improve lung function. Treatment is with standard regimens of anti–TB chemotherapy.

Intra-pleural fibrinolytics via IC tube with chest physiotherapy and mobilization of patients have often been used with success. Difficult cases will require surgical intervention. Decortication at open surgery or as a VATs procedure will be the procedures of choice.

11.7.4 References

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Chapter 12: HIV and EPTB

12.1 Introduction

TB is the most common opportunistic infection associated with HIV infection and represents the leading cause of death in these patients globally. TB infection in an HIV infected person can occur at any CD4 cell count, although the risk increases with progressive immunodeficiency. Even with effective ART, the risk of TB disease among people with HIV remains greater than that among the general population.

While pulmonary TB is more common than EPTB in HIV patients, extrapulmonary involvement in particular has been associated with advanced HIV infection with severe immunodeficiency thus considered as an AIDS defining stage 4 disease by the World Health Organization (WHO).

12.2 Clinical Presentations of EPTB in HIV

The commonest forms include lymph node (especially cervical and axillary), pleural (usually one-sided pleural effusion) and disseminated TB (disease that is not limited to one site in the body).

Pericardial and CNS TB are less frequent forms of EPTB but are more likely to result in fatal outcomes.

The commonest presentation of TB in the CNS is TBM. Less commonly it can manifest as tuberculous encephalitis, intracranial tuberculomas or tuberculous brain abscess.

EPTB of gut, genitourinary system and musculoskeletal system are also less frequently seen among HIV patients.

More severe and invasive disease is seen commonly among patients with CD4 cell counts of less than 250 cells/mm3 while the disease progression also shows a marked difference compared with patients with higher CD4 cell counts.

12.3 Clinical features

In patients who are markedly immune-suppressed, EPTB can be a severe systemic disease with high fevers, rapid progression, and features of sepsis. Clinical manifestations of EPTB in people with HIV are not substantially different from those described in persons without HIV. TB must be considered in disease processes involving any site of the body in an HIV infected patient especially in patients with CNS disease, when early TB treatment is essential to improve outcomes

Symptoms may be sub acute or acute with rapid progression and death. The clinical manifestations are variable, but often reflect the organs involved. Fever, weight loss, anorexia and malaise have been documented as the most common symptoms reported by patients with EPTB regardless of the site of the disease though this constitutional syndrome alone has a poor positive predictive value for the diagnosis.

12.4 Diagnosis

The diagnosis of extrapulmonary TB is challenging in HIV infected patients due to lack of pulmonary findings in advanced immunosuppression and manifestation of disseminated TB as non-specific febrile illness. Further, it is important to keep in mind possible mimickers of TB as establishing a confirmed diagnose of EPTB in PLHIV is difficult. EPTB should be suspected among all people living with HIV(PLHIV) presenting with pulmonary TB and symptoms suggesting specific organ involvement, such as breathlessness (pleural effusion or pericarditis), enlarged glands in the neck or axilla (lymphadenitis) and chronic headache or altered mental status (meningitis).

Initial diagnostic testing for EPTB disease should be directed at the anatomic site of symptoms or signs (e.g., lymph nodes, urine, cerebrospinal fluid). However, initial evaluation should always include chest imaging, even in the absence of pulmonary symptoms or signs. However, chest radiography is not a perfect screening tool for pulmonary TB, particularly among patients with advanced immunodeficiency who can have TB culture-positive sputum despite normal chest radiographs. Therefore, sputum smear, Nucleic Acid Amplification Test (NAAT), and culture should be performed in PLHIV with symptoms of TB disease who have a normal chest radiograph, as well as in persons with no pulmonary symptoms but evidence of TB disease elsewhere the body. NAAT is more reliable first line diagnostic tool due to paucibacillary

nature of the disease in HIV-MTB confection. NAAT Though the smear positivity depends on immunodeficiency status, culture is not affected by degree of immunodeficiency in HIV.

Positive Mantoux test (>5mm) with a low CD4 cell count requires an extensive investigation to exclude active TB even in the absence of specific symptoms and signs.

12.4.1 TB Lymphadenitis

In PLHIV lymph node TB can be diagnosed by combined yield of histopathology, smear, and culture from needle aspirates of enlarged lymph nodes like in non-HIV infected persons. However histopathologic findings are affected by the degree of immunodeficiency. Persons with relatively intact immune function have typical granulomatous inflammation associated with TB disease while with progressive immunodeficiency, granulomas become poorly formed or can be completely absent. If lymphadenitis is suspected, WHO-recommended Rapid Molecular Diagnostic tests (mWRDs) for samples obtained from lymph node biopsies or fine needle aspiration. Lateral Flow urine lipoarabinomannan assay (LF-LAM) may also assist in the diagnosis among PLHIV with low CD4 cell counts specially in countries with high HIV/AIDS burden.

12.4.2 CNS TB

The main investigations to diagnose CNS TB in PLHIV are cranial imaging (MRI) and lumbar puncture for CSF analysis. Mainly mononucleate cell (lymphocytic predominant) pleocytosis can be seen in TBM but in advanced HIV, CSF can be acellular. Low CSF glucose levels (usually less than 2.5 mmol/L) and high protein levels, typically between 1 and 5 g/L, are also suggestive of TBM.TBM need to be confirmed with either NAAT or TB culture done from CSF sample. The WHO recommendation is to use Xpert MTB/RIF Ultra which has a higher sensitivity than Xpert MTB/RIF as the preferred initial test for diagnosis of TB meningitis instead of conventional tests. ADA measurement can also be of use in the diagnosis of TB meningitis. Levels in CSF are significantly elevated in TBM (refer CNS TB in chapter 5).

12.4.3 Pleural TB

The diagnosis of TB pleuritic is made most often based on the pleural fluid full report with an elevated ADA level.

Further if *M. tuberculosis* is identified either by microscopy and/or culture in sputum and there is co-existent pleural effusion the diagnosis can be made by assumption

A confirmation of TB effusion is made by detection of MTB in pleural fluid or pleural biopsy specimens.

But Microscopy for AFB in the pleural fluid can identify *M. tuberculosis* only in approximately 20% of PLHIV with pleural TB; the yield can be up to 50% if the patient's CD4+ cell count is less than 100 cells/mm3. TB PCR/NAAT has a low sensitivity for diagnosis of pleural TB though it has a higher specificity

Histological sampling of the pleura with a blind biopsy or thoracoscopy and demonstration of caseating granulomas together can also be taken into consideration for the diagnosis of TB pleuritis.

12.4.4 Disseminated TB

Samples for microscopy for AFB and TB culture, as well as histology in combination with molecular biological techniques are needed for diagnosis of disseminated TB.

The accuracy of molecular biological tests for diagnosis of TB in non-respiratory specimens is reported in many studies and support their use in diagnosis of extrapulmonary TB. The urine lateral flow lipoarabinomannan (LF-LAM) assay is a point-of-care test for active TB and shows highest sensitivity in individuals with a CD4+ cell count <100 cells/mm^3 and it represents a useful adjunctive diagnostic for individuals with severe immune deficiency and in those who present with serious illness of unknown cause.

Mycobacterial blood culture has also proven useful in diagnosis of disseminated TB in patients with low CD4+ cell counts (sensitivity 20–40%)

Special note on Nucleic Acid Amplification Tests (NAAT) testing in HIV patients

NAAT tests provide rapid diagnosis of TB, and some assays like Xpert® MTB/RIF, and Xpert® Ultra also provide rapid detection of drug resistance simultaneously. Positive NAAT assays are highly predictive of TB disease when performed on Acid-Fast Bacillus (AFB) smear-positive specimens. However, because NTM infections may occur in PLHIV with advanced immunodeficiency, negative NAAT results in the setting of smear-positive specimens may indicate NTM infection and can be used to direct therapy and make decisions about the need for respiratory isolation.

NAAT tests are more sensitive than AFB smear, being positive in 50 to 80 percent of smear negative, culture-positive TB. Therefore; it is recommended that for all patients with suspected pulmonary TB, a NAA test be performed on at least one specimen. NAA tests also can be used on extrapulmonary specimens but the sensitivity is often lower than that of sputum specimens. Xpert® Ultra has higher sensitivity than Xpert® MTB/RIF and varied by specimen with higher yield from lymph nodes (96%), cerebrospinal fluid (85%), and gastric aspirates (78%) and lower yield from pleural fluid (34%) and other non-pleural serous fluids (67%).

12.5 Treatment of EPTB in HIV

Recommendations for anti-TB treatment regimens in PLHIV follow the same principles as for adults without HIV infection. In PLHIV with extrapulmonary TB, a 6- to- 9month regimen (2 months of INH, RIF, PZA, and EMB followed by 4 to 7 months of INH and RIF) is recommended**.** Exceptions to the recommendation for a 6 –to- 9month regimen for extrapulmonary TB include CNS disease (tuberculoma or meningitis) and bone and joint TB, for which many experts recommend 9 to 12 months**.**

DOT monitored by trained health care workers, who can be community-based or clinic-based, is recommended for all PLHIV with TB. Although intermittent dosing (twice- or thrice-weekly) would facilitate DOT, they have been associated with an increased risk of treatment failure or relapse with acquired drug resistance to the rifamycin class, particularly in PLHIV. Therefore, daily therapy given as DOT is recommended during both the intensive and continuation treatment phases for PLHIV.

Table 12: WHO Recommended Rapid Diagnostic tests as initial tests for diagnosis of TB

Diagnostic test	Pulmonary TB sample	Extrapulmonary TB sample	Rifampicin resistance	INH resistance
Xpert MTB/RIF	All adults and children with signs and symptoms: Sputum, gastric aspirate, nasopharyngeal aspirates, stool	Meningitis: cerebrospinal fluid Lymphadenopathy: lymph node aspirate, Lymph node biopsy Disseminated TB: Blood Other extrapulmonary: Pleural fluid or Peritoneal fluid or Pericardial fluid or Synovial fluid or Urine	Yes	No
Xpert MTB/RIF Ultra	All adults and children with signs and symptoms consistent with TB; includes PLHIV. Sputum, nasopharyngeal aspirates	Meningitis: cerebrospinal fluid Lymphadenopathy: lymph node aspirate, Lymph node biopsy	Yes	No
Urine LF-LAM	People living with HIV only (adults, adolescents and children) with signs and symptoms or advanced HIV disease or low CD4 count Urine	People living with HIV only (adults, adolescents and children) with signs and symptoms or advanced HIV disease or low CD4 count Urine		

(WHO: 2021)

12.5.1 The use of adjuvant steroids in the treatment of TB meningitis and pericarditis

Adjunctive corticosteroid therapy is recommended in individuals with HIV who have TB involving the CNS and should include dexamethasone (0.3–0.4 mg/kg/day for 2–4 weeks, then taper by 0.1 mg/kg per week until dose of 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week) for a total duration of 12 weeks or prednisone 1 mg/kg for 3 weeks, then tapered for 3-5 weeks.

12.5.2 Initiation of ART in EPTB/HIV

In TB/HIV co-infection, priority is to treat TB. TB treatment should be commenced first and ART commenced subsequently as soon as possible but within the first 2 weeks of starting anti TB treatment irrespective of the CD4 count, except for patients with signs and symptoms of TB meningitis. For PLHIV with TB meningitis, ART should be delayed at least by four weeks (and initiated within eight weeks) after treatment for TB meningitis is initiated. Adjunctive corticosteroid therapy is not recommended in the treatment of TB pericarditis (TBP).

12.5.3 Drug Interaction Considerations

As TB is the commonest co-infection among PLHIV, ATT are commonly used along with ARTs.

Most interactions between ART and ATT are through induction or inhibition of metabolic enzymes in the liver and intestine. The most important family of enzymes is CYP450.

Rifampicins are potent inducers of CYP3A4 and have clinically important interactions with Protease Inhibitors (PIs), Non-Nucleoside Reverse Transcriptase Inhibitors [NNRTIs], CCR5 inhibitors and Integrase Inhibitors. There are no major interactions between Rifampicin or Rifabutin and Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs).

Because of its potency, simplicity, and proven clinical efficacy, use of Efavirenz (EFV) 600mg with 2 NRTIs, is the preferred ART regimen for co-treatment of HIV and TB where rifampicin is part of ATT. If Efavirenz cannot be given, Raltegravir/Dolutegravir can be considered. Rifampicin is known to significantly lower plasma concentrations of Dolutegravir, and increasing the dose to a twice daily schedule is necessary.

Table 13: Recommendations for Anti –TB Drugs with ARV Drugs

TB Drug	ARV Drugs	Daily Dose
Isoniazid	All ARVs	5 mg/kg (usual dose 300 mg)
Rifampin **Note:** DTG, RAL and MVC doses need to be adjusted when used with rifampin.	HIV. PIs, DOR, ETR, RPV, BIC, CAB, or EVG/c	**Not recommended**
	TAF	Use with caution at dose indicated below.
	All other ARV drugs	10 mg/kg (usual dose 600mg)
Rifabutin **Note:** DOR and RPV doses need to be adjusted when used with rifabutin.	PI with COBI, TAF, RPV (MI), BIC, CAB, EVG/c-containing regimens	**Not recommended**
	DTG, RAL, DOR, EFV, or RPV (PO only)	5 mg/kg (usual dose 300 mg)
	HIV PIs with RTV	150 mg daily
	EFV	450-600 mg
Pyrazinamide	All ARVs	**Weight-based dosing** • *Weighing 40-55 kg: 1,000 mg (18.2-25.0 mg/kg)* • *Weighing 56-75 kg: 1,500 mg (20.0-26.8 mg/kg)* • *Weighing 76-90 kg: 2,000 mg (22.2-26.3 mg/kg)* • *Weighing >90 kg: 2,000 mg*
Ethambutol	All ARVs	**Weight-based dosing** • *Weighing 40-55 kg: 800 mg (14.5-20.0 mg/kg)* • *Weighing 56-75 kg: 1,200 mg (16.0-21.4 mg/kg)* • *Weighing 76-90 kg: 1,600 mg (17.8-21.1 mg/kg)* • *Weighing >90 kg: 1,600 mg*

(Centre for Disease Control and Prevention, USA: 2022)

When PLHIV with TB are receiving boosted PI, Rifampicin may need to be substituted with Rifabutin. If Rifabutin is not available, LPV/r can be used for the duration of TB treatment by doubling the standard dose of LPV/r to 800/200 mg.

For children, using triple NRTI (AZT+3TC+ABC) regimens also could be considered.

There is limited information on drug interactions between ART and new anti-tuberculosis drugs such as Bedaquiline and Delamanid, used extensively in drug-resistant or multi drug-

resistant (XDR/MDR) TB. As Bedaquiline is primarily metabolized by CYP3A4, concomitant use of EFV and PIs can interfere with drug concentration.

12.5.4 Adverse Effects of commonly used drugs for HIV/TB co-infected patients

1. Rash, fever, and hepatitis are common side effects of ATT drugs especially rifampicin, INH and pyrazinamide. NNRTIs and co-trimoxazole cause similar adverse reactions. Physicians have to face difficult clinical management decisions if these side effects occur in a patient on both ATT and ART.

2. PLHIV to be started on ~~A~~TT and ART needs liver function tests prior to the start of ART/ATT treatment and need to be rechecked at 2 weeks after starting ART/ATT and then monthly till completion of ATT.

3. Hepatotoxicity is a common and potentially serious adverse event. It is defined as

a. Serum AST or ALT more than three times of the upper limit of normal in the presence of symptoms or
b. Serum AST or ALT more than five times of the upper limit of normal in the absence of symptoms.

12.5.5 TB Immune Reconstitution Inflammatory Syndrome (IRIS)

In HIV infection, an exaggerated inflammatory reaction to *Mycobacterium tuberculosis* sometimes occurs when the immune system begins to recover following treatment with ART and known as TB IRIS**.**

TB IRIS occurs in two forms:

1. Unmasking IRIS refers to the flare-up of an underlying, previously undiagnosed TB infection soon after ART is started;

2. Paradoxical IRIS refers to the worsening of a previously treated TB infection after ART is started.

The management of IRIS may require corticosteroids, sometimes for prolonged periods, in order to control symptoms. There is no consensus on the optimal effective dose to use, although prednisone or methylprednisolone have been used at 1–1.5 mg/kg, with gradual reduction after 1–2 weeks. Individuals who have been on rifampicin for 2 weeks or more will have increased

corticosteroid metabolism in the liver, may require steroids for prolonged periods of time and IRIS may recur when the dose is reduced, necessitating higher doses. Physicians should be aware of the metabolic adverse effects and potential for serious infections, for instance local and systemic viral infections such as CMV retinitis or Kaposi sarcoma, with high-dose corticosteroids.

Recurrent needle aspiration to remove pus and caseous material is appropriate if lymph nodes or abscesses become tense and/or inflamed. This can prevent spontaneous rupture, which may lead to long-term sinus formation and scarring.

12.6 Follow-up

Close collaboration of the Chest clinic and STD clinic team is of utmost importance during follow up of these patients. Further it is important to keep close observation of HIV patients on treatment for CNS TB for possible paradoxical IRIS as this may lead to life threatening complications.

The following investigations should Ideally be carried out prior to commencement of Anti TB therapy

Nonetheless delay in obtaining these reports should not delay the commencement of treatment as soon as a diagnosis is made and the reports should be traced at the earliest.

• HIV plasma viral load and CD4+ cell count;
• Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT), bilirubin and alkaline phosphatase;
• Serum creatinine and estimated GFR;
• Platelet count;
• Hepatitis B and C serology;

PLHIV are at higher risk of drug reactions, especially those with low CD4+ cell counts, and are also more likely to have hepatitis B and/or C than HIV-negative individuals. Furthermore, they may be starting concomitant ART and other therapies, all of which may cause liver enzyme elevation and/or hepatotoxicity. Therefore, it is suggested that liver function tests should be rechecked at 1–2 weeks. Individuals with pre-existing liver disease need close monitoring, for instance every 2 weeks for the first 2 months. Most physicians will see the

patient 2 weeks after starting anti-TB therapy and then monthly until stable and 1–2 monthly until therapy has been completed.

In patients with extra-pulmonary TB, obtaining follow-up specimens can be challenging, making it difficult to assess the bacteriologic response to therapy. Instead, response typically is measured by an improvement in clinical and radiographic findings, but the frequency of such evaluations will depend on the infected sites, the severity of disease, and the ease with which specimens can be obtained.

Drug interactions between first line anti TB and antiretroviral drugs

Table 14 : British HIV Association (BHIVA) guidelines for the management of TB in adults living with HIV 2018 (2023 interim update)

	Ethambutol	Isoniazid	Pyrazinamide	Rifabutin	Rifampicin	Notes
Abacavir	◆	◆	◆	◆	■	Potential mild decrease in abacavir exposure due to increased glucuronidation with rifampicin; use standard doses of both drugs
Atazanavir	◆	◆	◆	■	●	Unboosted atazanavir is contraindicated with rifampicin (atazanavir exposure ↓80%) If using rifabutin, reduce rifabutin dose to 150 mg od; monitor for rifabutin toxicity
Atazanavir/r	◆	◆	◆	■	●	Boosted atazanavir is contraindicated with rifampicin If using rifabutin, reduce rifabutin dose to 150 mg od, or 300 mg x3/week; monitor for rifabutin toxicity
Atazanavir/c or darunavir/c	◆	◆	◆	■	●	Cobicistat is contraindicated with rifampicin; monitor for rifabutin toxicity
Bictegravir	◆	◆	◆	●	●	Cannot be used with rifabutin or rifampicin
Darunavir/r	◆	◆	◆	■	●	Has not been studied with rifampicin – modelling and simulations suggest higher darunavir/r doses could potentially overcome rifampicin induction but safety data are lacking and the combination is not recommended If using rifabutin, reduce rifabutin dose to 150 mg od, or 300 mg x3/week; monitor for rifabutin toxicity
Dolutegravir	◆	◆	◆	◆	■	Rifampicin decreased dolutegravir exposures by 54%; increasing dolutegravir dose to 50 mg bd has been used in limited clinical studies and is recommended Rifabutin has no clinically significant effect on dolutegravir; use standard doses of both drugs
Doravirine	◆	◆	◆	■	●	Give 100 mg bd doravirine with rifabutin
Efavirenz	◆	◆	◆	■	■	Efavirenz can be prescribed at standard doses with rifampicin, regardless of ethnicity or weight. Weight-based dose increment of efavirenz is no longer recommended with rifampicin. However, reduced doses of efavirenz 400 mg od is not recommended If using rifabutin, increase rifabutin dose to 450 mg od to compensate for

Table 15: BHIVA guidelines for the management of TB in adults living with HIV 2018 (2023 interim update)

BHIVA British HIV Association

BHIVA guidelines for the management of TB in adults living with HIV

	Ethambutol	Isoniazid	Pyrazinamide	Rifabutin	Rifampicin	Notes
						reduced exposure due to efavirenz; monitor for rifabutin toxicity
Elvitegravir/c	◆	◆	◆	■	●	Cobicistat is contraindicated with rifampicin Caution with rifabutin. Elvitegravir C_{trough} decreases by 67%. If using rifabutin, reduce rifabutin dose to 150 mg od; monitor for rifabutin toxicity and HIV treatment response
Emtricitabine	◆	◆	◆	◆	◆	No significant drug interactions anticipated
Enfuvirtide	◆	◆	◆	◆	◆	No significant drug interactions anticipated
Etravirine	◆	◆	◆	■	●	Use of rifampicin should be avoided. Reduced etravirine exposures but successful virological suppression with etravirine 200 mg bd and rifampicin were observed in a case report Etravirine can be administered at standard doses (in the absence of a second enzyme inducer) with rifabutin. Etravirine exposure ↓ 37% – monitor virological response
Lamivudine	◆	◆	◆	◆	◆	No significant drug interactions anticipated
Lopinavir/r	◆	◆	◆	■	●	Use of rifampicin not recommended. However, doubling the dose of lopinavir/r (e.g. 800/200 mg bd) or 'super boosting' with ritonavir (e.g. 400/400 mg bd) has been used in adults, and additional ritonavir boosting in children. Monitor for liver and gastrointestinal toxicity. Lopinavir/r od is contraindicated with rifampicin If using rifabutin, reduce rifabutin dose to 150 mg od. Dose of rifabutin 300 mg x3/week with lopinavir/r has been associated with subtherapeutic rifabutin exposure and development of rifamycin mono-resistance; monitor for rifabutin toxicity

Table 16: BHIVA guidelines for the management of TB in adults living with HIV 2018 (2023 interim update)

BHIVA British HIV Association

BHIVA guidelines for the management of TB in adults living with HIV

	Ethambutol	Isoniazid	Pyrazinamide	Rifabutin	Rifampicin	Notes
Maraviroc	◆	◆	◆	■	■	Rifampicin reduces maraviroc exposure by 60–70% (note: maraviroc was dosed at 100 mg bd in this study, and the magnitude of drug interaction with full-dose maraviroc is unknown). Maraviroc should be dosed at 600 mg bd with rifampicin. Maraviroc should be avoided with rifampicin in individuals also taking another enzyme inducer (e.g. efavirenz, nevirapine or etravirine), or in those with an estimated glomerular filtration rate of <30 mL/minute or on haemodialysis No clinically significant interaction was observed between maraviroc and rifabutin; use standard doses of both drugs (note: maraviroc and rifabutin doses should be reduced in the presence of a PI or cobicistat)
Nevirapine	◆	◆	◆	■	●	Use of rifampicin is not recommended (label states contraindicated). Nevirapine levels ↓ 20–55%, and the CARINEMO Study failed to demonstrate non-inferiority against efavirenz. If starting nevirapine in a patient established on rifampicin, do not use lead-in dosing Rifabutin should be used with caution in individuals on nevirapine. In contrast to efavirenz, nevirapine increased rifabutin exposure by 17%; standard doses of both drugs should be administered
Raltegravir	◆	◆	◆	◆	■	In a pharmacokinetic substudy of REFLATE TB, 400 mg bd raltegravir given with rifampicin showed high intra- and inter-individual variability and the 12-hour concentration was reduced by 31%. In Reflate 2 TB, the clinical outcome using this dose was inconclusive No clinically significant interaction was observed between raltegravir and rifabutin; use standard doses of both drugs
Rilpivirine	◆	◆	◆	●	●	Rilpivirine is contraindicated with rifampicin Rifabutin decreased rilpivirine exposure by 46%, and the combination is not recommended (contraindicated in US prescribing information). Increased doses of rilpivirine 50 mg od should be used (European Supplementary Protection Certificate [SPC])

Table 17: BHIVA guidelines for the management of TB in adults living with HIV 2018 (2023 interim update)

BHIVA British HIV Association

BHIVA guidelines for the management of TB in adults living with HIV

	Ethambutol	Isoniazid	Pyrazinamide	Rifabutin	Rifampicin	Notes
Tenofovir alafenamide	◆	◆	◆	■	■	Rifampicin may reduce tenofovir alafenamide bioavailability through transporter (P-gp) induction and is not recommended (note: administration of tenofovir alafenamide or tenofovir disoproxil fumarate with cobicistat is contraindicated because of rifampicin induction of cobicistat metabolism) Rifabutin expected to reduce tenofovir alafenamide exposure through P-gp induction; the combination is not recommended
Tenofovir disoproxil fumarate	◆	◆	◆	◆	◆	No clinically significant interaction with rifampicin (tenofovir exposure reduced by 12%) No clinically significant interaction with rifabutin (not studied)
Zidovudine	◆	◆	◆	◆	■	Rifampicin increases clearance of zidovudine, reducing plasma exposure by 47%. Use with caution (European SPC: 'avoid'; US prescribing information: 'dose modification not warranted')

Key to symbols: ●, these drugs should be not be co-administered; ■, potential interaction – may require close monitoring, alteration of drug dosage or timing of administration; ◆, no clinically significant interaction expected.

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Chapter 13: SPECIAL CONDITRIONS AMONG PAEDIATRIC AGE

13.1 Introduction

EPTB is observed more frequently in children compared with adults. Children, especially the younger age group are more likely to develop EPTB, including TB meningitis, disseminated and miliary disease due to high the risk of lympho-hematogenous spread.

Age is the single most important determinant of progression to active TB and disseminated disease in otherwise healthy children. The relatively immature immune system in the younger age group, especially less than 5 years, and age-related differences in the immune response to *Mycobacterium tuberculosis* contribute to this higher risk. The average risk for progression to active TB disease following a primary infection is 40%, 10%, 5%, and 2 % in age groups <1 year, 1-2 years, 2-5 years, and 5-10 years respectively. Most importantly, the average risk for TB meningitis or disseminated disease in the same age groups is 20%, 2-5%, 0.5%, and <0.5% respectively. This leads to very high mortality and morbidity including permanent disabilities in the younger population. Therefore, special attention should be paid on prevention (through active contact tracing and TB preventive therapy), early identification (through a high degree of suspicion and prompt investigations), and adequate treatment for both pulmonary and extrapulmonary TB in children.

About 20% of all children with TB have EPTB. The most common extrapulmonary manifestation is tuberculous lymphadenopathy (67%), followed by meningitis (13%, occurring most often in infants and toddlers), pleural TB (6%), miliary TB (5%), and skeletal TB (4%). In teenagers' lymph nodes, pleural spaces, and bones are commonly affected.

In over 90% of instances, active TB (both pulmonary and extrapulmonary) develops in children within the first 2 years of primary infection while a substantial proportion of them develop the disease within the first year of infection. Most children develop active TB as a progressive primary disease and reactivation or reinfection is not a common occurrence in children, especially in the younger age group.

The rates of EPTB are higher in children with immunodeficiency disorders. Some primary immune deficiencies involving T cell functions and phagocytic defects possess the highest risk. Although the numbers are relatively low, managing these children is challenging due to persistent or recurrent disease manifestations and relatively poor response to routine

management options. In addition, malnourish children also have an additional risk of developing EPTB and disseminated disease.

Important differences in comparison to adults and special areas to be highlighted in children with EPTB will only be discussed in this chapter. The rest of the common information including investigations and management of EPTB in children and adults are available in the other chapters of this guideline.

13.2 Clinical presentation and diagnosis of EPTB in children

TB in children has unique features which differ from adults and hence make the diagnosis more difficult. The symptoms of TB in children have a broad spectrum changing from non-specific symptoms to severe clinical presentations. TB may mimic many other common disease entities in children. Therefore, the variable and nonspecific clinical presentation is an important diagnostic challenge in children with EPTB which may ultimately to a late diagnosis and poor treatment outcomes.

The spectrum of clinical manifestations in children with EPTB is varied according to the affected organ and level of the immune response.

Importantly, accompanying extrapulmonary organ involvement may also be observed in some children diagnosed with PTB. Therefore, extra attention should be paid to identifying extrapulmonary organ involvement in these children. This vigilance is important to decide on the total duration of treatment and to prevent complications.

Adding to the burden of delay in the diagnosis due to nonspecific clinical manifestations, the sensitivity of diagnostic tests is also low in children due to paucibacillary disease and difficulty in obtaining proper and adequate samples.

In children suspected to have EPTB, Xpert MTB/RIF Ultra is recommended as the first line of investigation. In addition to the respiratory samples, fine needle aspiration or biopsy samples of lymph nodes, biopsy samples of any other tissue, CSF, and joint aspirates can be sent for Xpert. The availability of Xpert MTB/RIF Ultra has further increased the diagnostic yield.

13.3 Management of EPTB in children

The most important factor that affects morbidity and mortality rates in children with EPTB is early initiation of treatment. Therefore, it is required to have a high degree of suspicion of

possible EPTB in children who do not respond to routine management. While taking a maximum effort to confirm the diagnosis of EPTB microbiologically, one needs to initiate treatment without delay after the assessment of clinical and radiologic findings together when it is difficult or not possible to prove the disease through laboratory findings.

There is no difference in the drug regimen and duration of treatment for EPTB in children and adults. Anti-TB medications are well tolerated by children. Routine assessment of liver functions before commencing ATT is not recommended in children unless there is a specific indication.

A 12-month course of ATT (2HRZE 10HR) is recommended for children with the CNS TB and osteoarticular TB. In all the other cases of EPTB, a 6-month regimen is routinely used. However, in children with primary immune deficiencies or disseminated disease, the duration might be extended on an individual basis. In some instances, such as children with mendelian susceptibility to mycobacterial diseases (MSMD), more prolonged courses of ATT or even lifelong prophylaxis might be required and the decisions should be taken by relevant specialists.

Due to the almost total lack of ocular toxicity in children of all ages receiving ethambutol at doses of 15-30 mg/kg, WHO has recommended that children of all ages can be given EMB in daily doses of 20 mg/kg. Therefore, ethambutol can be used without any restriction for treating children with EPTB of all ages.

Streptomycin is no longer recommended as a treatment option for drug-susceptible TB in children due to its potential risk of irreversible ototoxicity, nephrotoxicity, and poor tolerability (intramuscular injection). Amikacin can be used as an alternative to streptomycin in situations such as bridging therapy for children who developed anti-TB drug-induced hepatotoxicity.

13.4 TB lymphadenitis

Lymph node disease is the commonest extrapulmonary manifestation of TB in children. Cervical lymph nodes are the most affected group of nodes. Painless cervical mass including multiple matted nodes is the most common presentation. Late diagnosis and initiation of treatment could be led to a prolonged and relapsing course. Spontaneous drainage with sinus formation is a possibility.

Persistent (> 2-4 weeks) cervical adenopathy without a visible local cause or proper response to first-line antibiotics and a cervical mass of ≥2 × 2 cm needs further investigations to exclude TB. A definitive diagnosis can be established minimally invasively by fine-needle aspiration biopsy (FNAB) and testing the sample with Xpert MTB/RIF Ultra. If the yield is poor, an excision biopsy is required for further evaluation.

A 6-month course of ATT (2HRZE 4HR) is sufficient for uncomplicated cases of TB lymphadenitis. In some children, lymph node size might be increased following apparent clinical improvement, a few weeks after starting treatment. This is usually due to TB IRIS and can be developed in both HIV-positive and negative children. A course of steroids while continuing the ATT is required in the management.

13.5 BCG adenitis

Live *Mycobacterium bovis* strain of BCG vaccine can induce local lymph adenopathy in some infants. The usual site is the ipsilateral axillary lymph nodes. Usually, the child is otherwise well and asymptomatic both clinically and radiologically. This is usually a self-limiting condition and hence, ATT is not required. Reassurance and follow-up would be sufficient at the initial stage.

If the clinical features are compatible with BCG adenitis, further investigations including needle aspirations and/or biopsy for Xpert and/or TB culture should **not** be done. Xpert MTB/RIF Ultra or routine TB culture facilities cannot differentiate *Mycobacterium bovis* from *Mycobacterium tuberculosis* and hence, the reports of obvious BCG adenitis will come as "positive for *Mycobacterium tuberculosis*". This could lead to unnecessary commencement of ATT while labelling as EPTB in children with self-limiting BCG adenitis.

13.6 Tuberculous meningitis (TBM)

TBM is the most severe manifestation of childhood TB. TBM is most commonly seen in young children (<3 years of age). Initial presentation is usually non-specific before the more advanced disease becomes apparent. Early diagnosis is essential to ensure an optimal outcome. Delay in initiation of treatment may lead to high mortality and permanent disabilities.

Symptoms and signs of the early disease include fever, listlessness, failure to thrive and headache in older children. When the disease progresses, localising neurological signs will

develop. In some children level of consciousness may be reduced intermittently or persistently. Some may present with generalized or focal convulsions.

Children with TBM may present as pyrexia of unknown origin (PUO) which often begins with a prodrome of constitutional symptoms such as lassitude, malaise, night sweats, and intermittent headache, to be followed by vague CNS symptoms such as behavioural changes, irritability, drowsiness, headache, vomiting and seizures.

Suspected pyogenic meningitis with the subacute onset and/or with features of raised intracranial pressure not responding to antibiotic treatment, should prompt one to think of possible TBM. Features that may help distinguish TBM from bacterial meningitis include a subacute presentation and the presence of neurologic signs especially cranial nerve palsies most frequently involving cranial nerves II and VI.

Most of these clinical features can be explained by the formation of a dense basal exudate leading to raised intracranial pressure and cerebral vasculitis with brain ischaemia/infarction, which are the key findings on brain imaging. Assessment of CSF is indicated to establish the diagnosis.

All children diagnosed with drug-susceptible TB meningitis (irrespective of bacteriological confirmation) should complete 12 months of a full course of ATT. Trials of TB treatment (using response to TB treatment as a diagnostic tool) are strongly discouraged. Once initiated, the TB treatment regimen should be continued until completion, unless a very clear alternative diagnosis has been established.

Steroids will reduce the organization and fibrosis of exudates and hence, it is recommended to use steroids in TB meningitis and other forms of CNS TB. The recommendation in children is 1-2mg/kg/day of prednisolone for 4 weeks to be tapered down over 1-2 weeks before stopping. Some children may need longer treatment with steroids, of up to 6–8 weeks. This decision should be made based on the disease severity and complications of TBM.

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Chapter 14: OTHER IMPORTANT SITES OF EXTRAPULMONARY TUBERCULOSIS

14.1 TUBERCULOSIS OF HEART

14.1.1 Tuberculous Pericarditis

Although tuberculous involvement in cardiovascular system is uncommon, it is described in 1-2% of the patients. The commonest site of involvement is the pericardium (TB Pericarditis-TBP). Even though patient with TBP found to have evidence of TB elsewhere in the body this may be the only site for TB involvement. It can present as;

1. Acute pericarditis
2. Pericardial effusion
3. Cardiac tamponade
4. Chronic constrictive pericarditis

Mortality rate of acute pericarditis more than 80% in acute stage and still higher in later stages. Normal amount of pericardial fluid in an adult is 15-50ml.Pericardial effusion is an abnormal accumulation of fluid in the pericardial cavity.

The pathogenesis of pericardial TB has been attributed to hematogenous spread from initial primary infection or later dissemination of reactivated disease, or contiguous spread from adjacent organs, such as mediastinal nodes, lungs, spine, and sternum or during miliary dissemination.

14.1.2 Stages of TBP

TBP may progress from one stage to the next or anyone or series of stages may be present without others.
Clinical features are generally nonspecific and subtle. The onset may be abrupt or insidious.

Table 18: Pathological changes and clinical features of stages of pericarditis

Stage	Pathological changes	Clinical features
1. Dry stage	Fibrinous exudate, Increased neutrophil, relatively high mycobacteria with early granuloma formation	Features of acute pericarditis with chest pain, pericardial friction rubs and widespread ST elevation without effusion.
2. Effusion stage	Serosanguinous effusion with lymphocytic predominance, high protein content and low bacterial load (most common form of TBP)	Symptoms of cardiac failure with or without evidence of cardiac tamponade due to moderate -large effusion.
3. Absorption stage	Absorption of effusion with granulomatous caseation and pericardial thickening with subsequent fibrosis.	Symptoms and signs of constrictive pericarditis. Radiological and Echo evidence of thick fibrinous fluid around the heart
4. Constrictive stage	Constrictive scarring. fibrosing visceral and parietal pericardium contracts on cardiac chambers may become calcified leading to constrictive pericarditis	Symptoms and signs of Classic syndrome of constrictive pericarditis 2D Echo – No residual fluid in pericardium.

Clinical features

- Fever (70-90%)
- Chest pain – central or left-sided (most often sharp pain or dull pain)
  - May radiate to neck, shoulder, or arm.
  - Worsen on deep breathing, coughing, swallowing, or lying flat.
  - Improved by sitting up, or leaning forward.
  - Note: ischemic pain does not worsen with deep breathing and not change with position.
  - Severe pericardial pain of acute onset is unusual
- Shortness of breath (almost always present)
- Cough
- Fatigue
- Night sweat

- Weight loss
- Chronic cardiac compression mimicking heart failure may be the common presentation
- Symptoms of constrictive pericarditis
  - Right upper abdominal pain
  - Ascites
  - Leg edema
  - Hypotension leading to malaise and dizziness
  - Weak pulse
  - Elevated Jugular Venous pressure (JVP)
  - Tachycardia
  - Muffled heart sound
  - Third heart sound
  - Pericardial friction rub
- Pulses paradoxes

Differential diagnosis for pericarditis

- TB
- Other bacterial, viral, or fungal infection
- Malignancy, Lymphoma, and Kaposi's Sarcoma
- Autoimmune diseases
- Uremia
- Radiotherapy
- Medication
- Trauma
- Idiopathic

The role of the cardiologist is pivotal in management of TBP

1. To determine the volume of the effusion
2. To detect any features of cardiac tamponade
3. To arrange pericardiocentesis if technically possible or clinically indicated
4. To assess the progression of the disease

14.1.3 Investigations

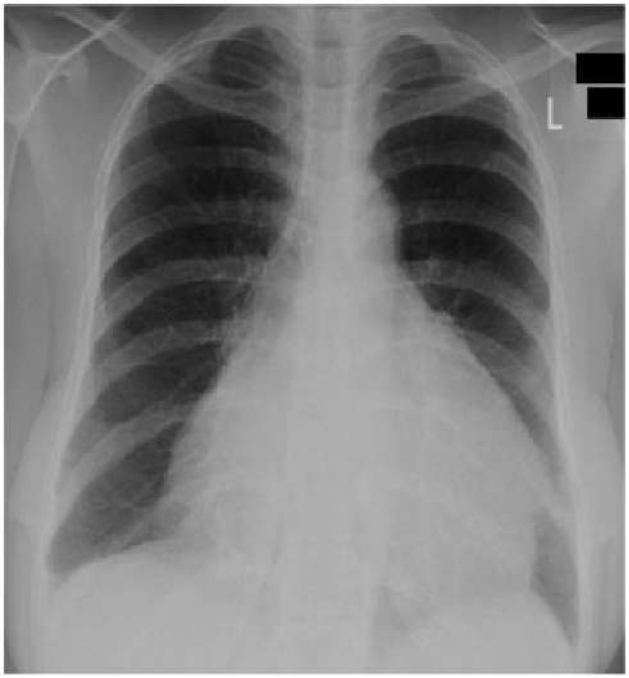
Imaging including radiographs and echocardiograms are non-diagnostic.

1. Sputum for AFB direct smear, Xpert MTB/RIF Ultra, AFB culture and DST (if there is evidence of pulmonary involvement) - positive in 10-55%
2. Chest radiography
3. ECG
4. 2D Echo
5. CT chest +/- MRI chest
6. If pericardiocentesis done send pericardial fluid for protein, differential count, AFB direct smear, AFB culture, Xpert MTB/RIF Ultra, cytology, ADA, LDH, and pyogenic culture.
7. Pericardial biopsy
    - Xpert MTB/RIF Ultra
    - AFB culture
    - Histology
8. Right scalene (supraclavicular) lymph node biopsy if enlarged for
    - Histology
    - AFB direct smear
    - AFB culture
    - Xpert MTB/RIF Ultra

Chest radiography (**Figure 11**)

- Enlarged cardiac shadow in more than 90% of cases (CTR >0.5)
- Features of active pulmonary TB in 30% of cases
- Pleural effusion 40-60%
- Pericardial calcification
- No hilar lymphadenopathy

Figure 11: Chest X-ray



CT and/or MRI chest

- Detection of pericardial effusion and pericardial calcification
- Thickening of pericardium
- Enlarged mediastinal lymph node (≥10mm) with matting and hypodense center with sparing of hilar lymph node.
- Mediastinal lymphadenopathy may not be visible in chest radiography even after pericardial fluid aspiration.
- No lymph node enlargement noted in viral or idiopathic pericarditis.
- Hilar lymph node involvement is prominent in patients with mediastinal lymph node enlargement due to lymphoma, malignancy and sarcoid.

Figure12: PR segment deviation with upward ST segment elevation

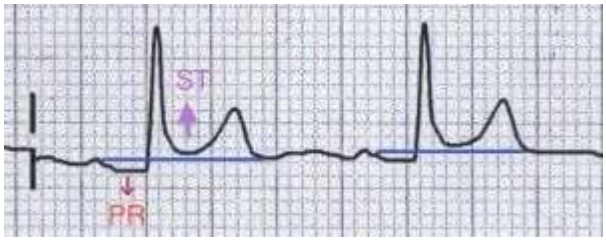


Figure 13: Presence of micro voltage (QRS complex <5mm in limb leads, <10mm in precordial leads) suggests large pericardial effusion

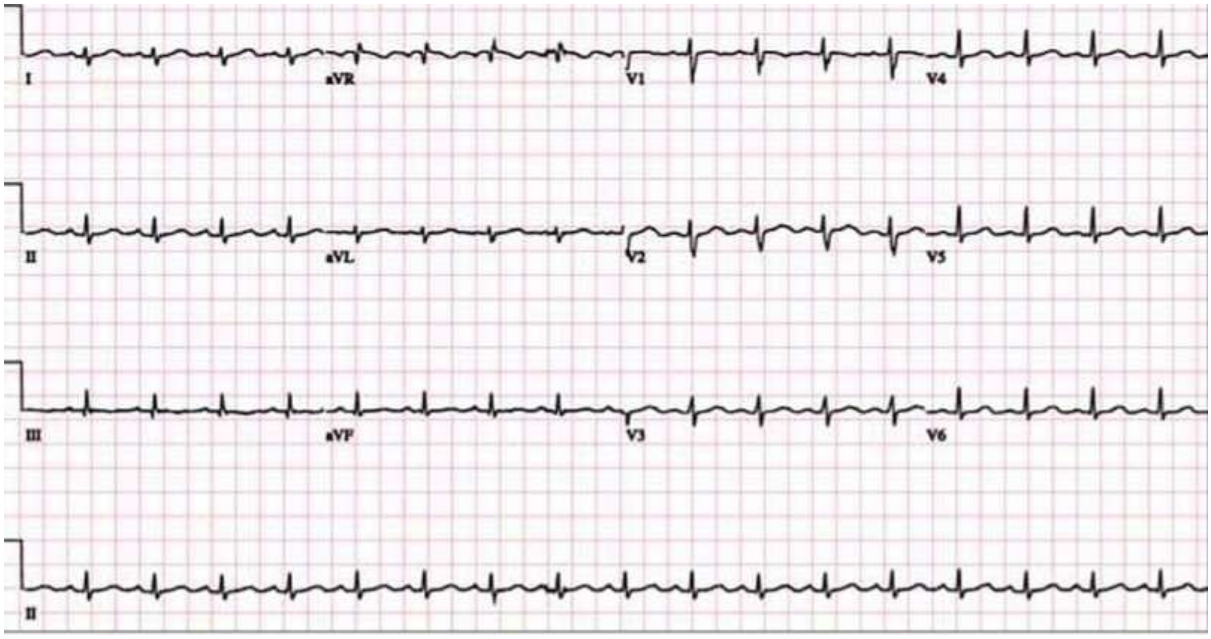
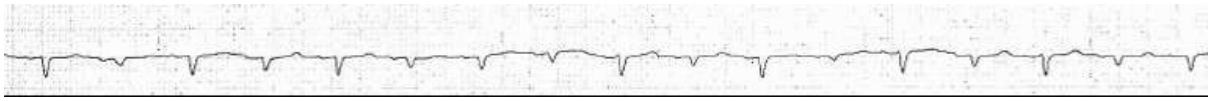


Figure 14: Electrical alternance (a marker of cardiac tamponade requiring urgent pericardiocentesis)



- Abnormal in almost all cases of TBP
- Usually nonspecific ST-T wave changes.
- Features of acute pericarditis such as PR segment deviation with ST segment elevation noted only in 9-11% of cases.
- Tachycardia
- Presence of micro voltage (QRS complex <5mm in limb leads, <10mm in precordial leads) suggests large pericardial effusion.
- Cardiac tamponade is unlikely if micro voltage (low voltage) is absent.
- Only 4% of cases had atrial fibrillation
- Electrical alternance (a marker of cardiac tamponade) is uncommon

Echocardiogram

- Large pericardial effusion with fibrinous strands (worm or frond-like projections) on visceral pericardium (up to 60%), thick "porridge-like" exudate suggestive of an exudate but not specific for TB pericardial effusion.
- Right ventricular collapse in cardiac tamponade.
- Calcified pericardium in TPE indicate later stage of the disease (also seen in cancer).
- No fibrinous strand in pericardial effusion due to viral disease, physiological pericardial effusion, or fluid overload.

Suspect TBP if;

- Immunocompromised
- Large heart shadow on CXR
- Increased JVP
- Pericardial rub
- Muffled heart sounds

Invasive Investigations

- ***Pericardiocentesis***

Recommended in all suspected patients for diagnostic purposes if, technically safe as decided by the consultant cardiologist.

Features of pericardial fluid

- Exudative high protein serous/ serosanguinous or hemorrhagic (mainly)
    - Differential diagnosis
        - Malignancy
        - Late effect of penetrating trauma
- High LDH
- High ADA
- Elevated leucocyte count (predominantly lymphocytes and monocytes)
- AFB direct smear positive in 0-42%
- AFB culture positive up to 75%
- AFB DS and GeneXpert positivity is very low

- ***Pericardial biopsy***

Useful when a definite diagnosis is not arrived. Or when pericardiocentesis is not possible. Cannot exclude the diagnosis of TB, and the sensitivity is variable.

Diagnostic criteria of TBP in TB endemic countries

a) Definitive TBP
   i. AFB Direct smear or Culture Positive in pericardial fluid, and / or
   ii. TB Bacilli or caseating granuloma in histology of pericardium

b) Probable TBP
   i. Evidence of pericarditis with TB elsewhere, and/or
   ii. Lymphocytic pericardial effusion with elevated ADA, and/or
   iii. Mediastinal (non-hilar) lymph node on chest CT with hypodense center and matting with positive skin tuberculin test.
   iv. Good response to Anti TB treatment.

14.1.4 Treatment of TBP

ATT has reduced the incidence of constrictive pericarditis (from 88% to 10-20%) and morality (from 80-90% to 8-17%) associated with tuberculous pericarditis.

Empirical treatment should be considered, especially in the immune compromised. In addition to ATT (6-month treatment regime), corticosteroids are recommended in patient with high risk of constrictive pericarditis.

As steroids may prevent constrictive pericarditis, it should be given to all HIV negative patients.

In HIV positive patients, steroids should be given in patients with highest risk for constrictive pericarditis.

- Patients with large effusion
- Those with high level of inflammatory cells in pericardial fluid
- Early signs of constriction (right ventricular collapse in echocardiogram)

14.1.4.1 Steroid regime for adults

- Without HIV infection:

Prednisolone dose – 1mg/Kg/day (max. of 60mg) for 4 weeks and gradually tailed off over 4-6 weeks.

- With HIV infection:

Steroids given as short-term treatment tapering over 4-6 weeks. Prednisolone dose is 1mg/Kg/day tapered by 10mg/day weekly.

14.1.4.2 Surgical management

- **Pericardiocentesis**

Compulsory if there is evidence of tamponade at diagnosis.

- Relieves symptoms
- Prevent constriction
- To prevent or treat tamponade
- It is recommended in suspected impending tamponade (severe dyspnea and resting tachycardia)

- **Pericardiectomy**

Timing to be decided by the thoracic surgeon and the cardiologist depending on the pathological stage and the response to Treatment. Early intervention may be advisable in advance pathological stages.

In situations where the effusions reaccumulate or central venous pressure remains persistently elevated despite removal of pericardial fluid and use of antituberculosis drugs and steroids, early pericardiectomy is suggested.

14.1.5 Follow up

2D Echo at 2 weeks and 6-8 weeks and at the end of treatment to detect the response to treatment or and to detect onset of constrictive pericarditis in order to refer for early surgery. Repeated imaging (CT, MRI) if clinically indicated intervals to ensure response to treatment and to detect any previously undetected pathology such as malignancy.

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14.2 TUBERCULOSIS AND MALIGNANCY

As TB and malignancy predispose each other, the co-existence of both will have worse outcomes if not diagnosed early and treated properly.

- Malignancy itself is an immunocompromised state which predisposes to active TB.
- Chemotherapy and immunotherapy cause extreme immunosuppression.
- Radiotherapy, surgery (e.g., gastrectomy leading to malnutrition) and other risk factors such as increasing age, male sex, medical conditions like diabetes, Chronic Renal Failure (CRF), and Chronic Lung Disease can contribute to reactivation of TB.
- Patients with malignancy – invasion of cancer cells into healed TB lesions leading to weakening of local immunity which might lead to reactivation of TBI (TB Infection or latent TB).

- The effect of radiation on the immune system by multiple factors such as local tissue damage, peripheral reduction of lymphocytes, and alternation in the immune cellular balance namely B-cells, T-cells, and natural killer cells predisposed to reactivation of TBI.
- TNF activity is required to maintain the integrity of granuloma. By suppressing the immune system, TNF-a inhibitor predisposed to TB reactivation.
- Several studies reported development of TB in patients during or after Immune Checkpoint Inhibitor (ICI) therapy (due to the use of high dose steroids or TNF- α inhibitor for immune related adverse events, and possibly due to drug itself).

Simultaneously, MTB causes chronic and persistent inflammation leading to DNA damage (by the production of nitric oxide and reactive oxygen species by mycobacterial cell wall components), apoptosis inhibition, and enhanced angiogenesis, resulting in an increased risk of cancer.

TB and malignancy clinically and radiologically mimic each other, which can lead to misdiagnosis and delay in initiating treatment.

Clinical features may be misleading in uncommon types of EPTB such as pancreatic TB, ovarian TB, or even TB lymphadenitis.

Unexplained deterioration of cancer patients could be due to infections including reactivation of TB. Fever, cough, increasing lymphadenopathy, poor response to treatment, new infiltrating lesions on chest radiograph or other imaginary studies favour suspicion of TB.

TST and IGRA may be falsely negative.

14.2.1 Diagnosis

Sputum AFB direct smear, Xpert MTB/RIF Ultra, AFB culture when pulmonary disease is suspected.

Bronchoscopy, EBUS, US/ CT guided, or surgical biopsy should be taken in normal saline for bacteriological studies (Xpert MTB/RIF Ultra and AFB culture) in addition to histology in formal saline.

14.2.2 Treatment

Standard ATT depending on the site of the involvement as per guidelines applicable at the time. Close monitoring for side effects has to be done. Recommencement of chemo, radiotherapy to be decided by the oncologist and the pulmonologist and the relevant consultant to ensure best chances of elimination of TB while not delaying anti-cancer treatment unnecessarily.

If the patient is already on treatment for cancer, it is advisable to withhold ICIs, TNF-α inhibitor, and other immunosuppressive drugs after discussion with oncologist and initiate ATT immediately. Cancer treatment may be restarted after about 2-4 weeks of initiating ATT. Special attention to drug interactions to ensure adequate blood levels of anti TB drugs is ensured. Continuous and adequate treatment of TB should be considered the priority.

14.2.3 Indication for latent TB infection, screening, and treatment

1. All cancer patients before initiating immunotherapy specially TNF-α inhibitors and ICIs.
2. Children with solid cancers and haematological malignancies.
3. As the risk of developing TB decreases over time since the initial diagnosis of cancer and/or the cumulative lifetime is reduced due to reduced life expectancy; screening should be done in adults, especially in haematological malignancy, who have one or more additional risk factors (such as contact history of active pulmonary TB, HIV, CRF, and diabetes).

LTBI treatment should be started 4 weeks prior to commencing TNF-α inhibitor however, it can be given at any time including concurrently with TNF-α inhibitor.

For ICIs, LTBI treatment should be started prior to therapy (such as before 2 weeks) in order to assume the patient's tolerance to anti TB prophylaxis.

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14.3 CUTANEOUS TUBERCULOSIS

Cutaneous TB results from skin infection with *M. tuberculosis*, the same bacterium that causes TB of the lungs. Of the 8-24% cases of EPTB, cutaneous TB accounts for about 1.5- 3% of cases. The immune response to the tubercle bacillus influences the clinical manifestations of infection. Prior infection with the tubercle bacillus or BCG vaccination results in moderate to high immunity. Drug-induced immunosuppression, use of TNF- α and systemic illness such as HIV/AIDS or leukemia may allow reactivation of latent TB. Even though the cutaneous TB represent a small proportion of extra-pulmonary cases, the number may be significant considering the high prevalence of TB in developing countries. Cutaneous TB frequently has systemic involvement.

14.3.1 Classification

The clinical spectrum of cutaneous TB is classified based on

- The route of infection- endogenous, exogenous
- The immune status of the patient
- Prior sensitization with TB
- Mycobacterial load

The classification is complex and not always satisfactory as the disease manifestations dependent on various factors such as host's cell mediated immunity and the route of infection.

1. Based on the route of infection

- **Exogenous**- Primary inoculation of the skin- usually following trauma
  - In non-immune host- Tuberculous chancre
  - In immune host- TB verrucosa cutis, lupus vulgaris

- **Endogenous route -** Contiguous spread from deeper structures (e.g., lymph node, bone & joint, epididymis)
  - to overlying skin- Scrofuloderma
  - Haematogenous spread- tuberculous gumma (abscess), miliary TB, Lupus vulgaris
  - Autoinnoculation –orificial TB (perioral, perianal)

2. Mycobacterial load

Multibacillary forms- abundant mycobacteria are present in the lesion- scrofuloderma, tuberculous chancre, acute miliary TB

Paucibacillary -mycobacteria are difficult to isolate - lupus vulgaris, TB verrucosa cutis, tuberculids.

Table 19: Classification of cutaneous TB

Host immunity (Multibacillary forms)	**Method of inoculation**	**Disease**
Naïve host	Direct inoculation	TB chancre (primary inoculation)
Low	Contiguous spread	Scrofuloderma
Low	Autoinoculation	Orificial TB
Low	Haematogenous spread	Acute miliary cutaneous TB
Low	Haematogenous spread	TB gumma (abscess)
Host immunity (Paucibacillary forms)	**Method of inoculation**	**Disease**
High	Direct inoculation	Warty TB (TB verrucosa cutis)
	Direct inoculation	

High High High	Haematogenous spread Immune reaction within the skin due haematogenous dissemination of *M. tuberculosis* or its antigens from a primary source	Lupus vulgaris-(some) Lupus vulgaris Tuberculids - Lichen scrofulosorum - Papulonecrotic Tuberculid - Erythema induratum (Bazin's)

14.3.2 Clinical features

Cutaneous TB has a wide range of clinical presentations. All cases of cutaneous TB require a careful evaluation of systemic involvement.

1. Primary inoculation TB (TB chancre)

This is due to the direct inoculation of *M. tuberculosis* into the skin in people without natural or artificially acquired immunity to the organism. The organism does not have the ability to penetrate the skin barrier and usually gains access when there are defects in the form of abrasions or minor injuries. These lesions contain many organisms (multibacillary) which is more common in children. Infection may follow piercings, tattooing, or other penetrating skin injury.

It develops 2-4 weeks after the inoculation and presents as a painless, firm, red-brown papulonodule that slowly enlarges. It eventually erodes to form a sharply demarcated ulcer with undermined edges. TB chancre most frequently develops in face, hands, and lower extremities. Regional lymphadenopathy usually develops after 4- 8 weeks and the complex of TB chancre and regional lymphadenopathy is analogous to Ghon focus in the lung. Sporotrichoid lesions with enlarged regional lymph nodes can develop. The lesion then heals within 3- 12 months leaving an atrophic scar and calcified regional lymph nodes.

2. Scrofuloderma

This results from the direct invasion of the tubercle bacillus into the skin from an underlying contiguous tuberculous focus.

Scrofuloderma begins as asymptomatic, bluish red, subcutaneous swellings (cold abscess) that persist for several months and break down to form undermined ulceration with soft granulating

tissue at the base. There is multiple sinus tract formation with drainage of purulent material that secondarily infect overlying dermis. After healing, characteristic puckered scarring marks the site of the infection.

Figure 15: Scrofuloderma

Discharging sinus and ulcerated plaque in a patient with cervical tuberculosis adenitis

3. Orificial TB

This results from auto inoculation of *M. tuberculosis* causing infection of the mucosa or skin adjacent to orifices most affected area being the oral mucosa. The patient will usually have advanced internal TB.

It is characterized by oedematous red papules that ulcerate with undermined edges. They are painful, resistant to treatment do not tend to heal spontaneously.

4. Acute miliary cutaneous TB (Disseminated cutaneous TB)

This is due to haematogenous spread of bacilli in to the skin and is rare. It is usually seen in advanced pulmonary or meningeal and disseminated TB and affects immunosuppressed patients.

The skin lesions are characterized by pinhead-sized, bluish-red papules capped by minute vesicles which later develop into central umbilication and crusting. They tend to heal with white scars.

5. Metastatic Tuberculous Abscess (TB Gumma)

This is also due to mycobacteremia with cutaneous seeding. It presents as single or multiple subcutaneous nodules or cold abscess on an extremity. It may become fluctuant ultimately the overlying skin breaks down to form an ulcer with sinus tracts and fistulae.

Unlike scrofuloderma, there is no involvement of underlying tissue.

6. TB verrucosa cutis

This is the result of exogenous inoculation of *M. tuberculosis* in previously infected or immune individuals with moderate- high degree of immunity. The lesions contain few organisms (paucibacillary) It begins as a small, asymptomatic, indurated wart-like papule with a subtle inflammatory rim. It gradually enlarges often in a serpigionous manner to form reddish brown verrucous plaque. The most affected sites are the hands, knees, ankles and buttocks. After several years the plaque can heal spontaneously.

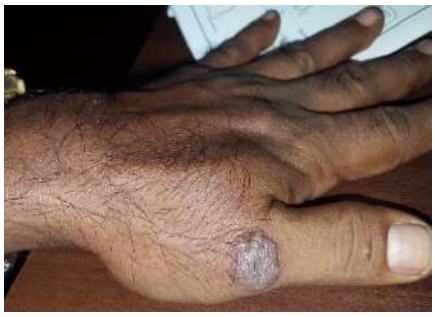

Figure 16: TB verrucosa cutis

A wart like plaque at the site of exogenous inoculation

7. Lupus vulgaris

Lupus vulgaris is one of the most prevalent forms of cutaneous TB and occurs in previously sensitized individuals. The lesions are acquired either by haematogenous spread from an underlying tuberculous focus or by direct innoculation. It can occasionally arise from BCG inoculation.

The lesion is ared-brown plaque composed of papulonodules with an “apple jelly” color on diascopy. The plaque enlarges with central scarring ultimatetely leding to significant tissue destruction. The head and neck region are the most affected site especially the nose, cheeks, and earlobes.

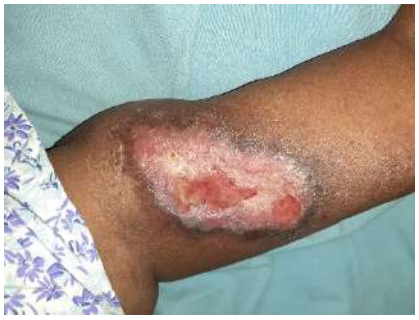

Figure 17: Lupus vulgaris

Erythematous plaque with scarring and central ulceration

Tuberculids

A group of disorders that classically associated with systemic TB. They are considered as immune reactions within skin due to hematogenous dissemination of *M. tuberculosis* or its antigens from a primary source, in an individual with strong antituberculous cell mediated immunity.

Often beginning as an immune complex mediated reaction and evolve into a granulomatous inflammatory response.

1.Lichen scrofulosorum

It is characterized by asymptomatic innumerable grouped erythematous perifollicular flat-topped papules, often with a variable scale, that have a predilection for the trunk and proximal extremities. Lesions may persist for months and disappear without scarring.

2.Papulonecrotic tuberculid

Recurring crops of painless polymorphic erythematous to violaceous papular, pustular and nodular lesions that are widely distributed in a symmetric pattern and favour the extensor aspects of the extremities and buttock. Heals with varioliform scarring and multiple cyclic eruptions are characteristic. Seen most frequently in children and young adults.

3.Erythema induratum of bazin

A form of lobular panniculitis with vasculitis. It is characterized by tender, erythematous subcutaneous nodules, commonly present on bilateral posterior calves that ulcerate. Predominantly affect young women.

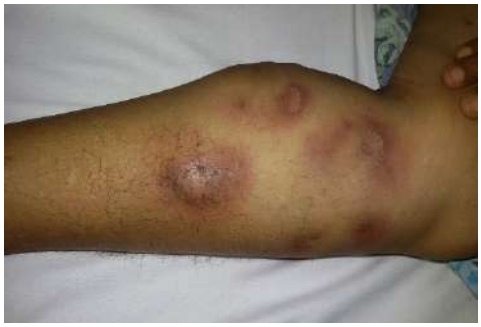

Figure 18: Erythema Induratum

Multiple subcutaneous nodules typically present on the backs of the legs

14.3.3 Diagnostic workup

A thorough diagnostic workup is required to identify systemic involvement.

The diagnosis of cutaneous TB is complex and requires high index of suspicion. Several laboratory investigations performed together are often required. These include isolation in culture, histopathology, demonstration of AFB on stains, positive TST, evidence of systemic TB and response to treatment. Although a positive culture provides a definite diagnosis, the sensitivity is low due to paucity of mycobacteria in skin lesions. Furthermore, non-specific histology presents an additional challenge in rendering a diagnosis. About 14 – 30% of cases do not have characteristic histology.

Table 20: Features of cutaneous TB

Classification	Cutaneous TB	Characteristic histopathology	Bacilli on acid fast stain	TST	IGRA
Cutaneous TB	Primary inoculation TB	Necrosis Dense neutrophilic infiltration	Numerous	Negative; may become positive in later stages	Positive
	TB verrucosa cutis	Pseudoepitheliomatous hyperplasia Epithelioid granuloma in the mid dermis	Usually, absent	Strongly positive	Positive

		Neutrophilic microabscesses may be present			
	Lupus vulgaris	Upper dermal epithelioid granulomas or confluent granulomatous infiltrate Caseous necrosis may be present Dermal fibrosis may be present	Uncommonly present	Commonly positive	Positive
	Active milliary TB	Necrosis Dense neutrophilic infiltration with abscess formation in the dermis	Numerous	Negative	Positive
	TB gumma	Diffuse granulomatous inflammation caseous necrosis in the deep dermis and subcutis	Commonly present	Negative or positive	Positive
	Orificial TB	Caseating granulomas in superficial to mid dermis	Numerous	Negative or positive	Positive
	Scrofuloderma	Ulcerated epidermis Suppurative granulomas Sinus tracts occasionally present	Commonly present	Usually positive. May be negative in some cases	Positive
Tuberculids	Lichen scrofulosorum	Periappendageal epithelioid granulomas	None	Strongly positive	Positive
	Papulonecrotic tuberculid	Leukocytoclastic vasculitis Wedge shaped necrosis	None	Strongly positive	Positive
	Erythema induratum	Lobular panniculitis Epithelioid granulomas may be present	None	Strongly positive	Positive

14.3.4 Treatment of cutaneous TB

Treatment is as same as that PTB. Tuberculids reactions resolve with the initiation of antituberculosis drug against the primary site of TB.

What is the outcome of cutaneous TB?

Spontaneous healing can occur for tuberculous chancre, scrofuloderma, and TB verrucosa cutis. Lupus vulgaris is usually progressive if untreated. Some presentations of cutaneous TB such as miliary TB indicate significant systemic disease which may be fatal.

Treatment is usually successful with an adequate course of appropriate multi-drug therapy, although some skin lesions are slow to heal.

Chapter 15: PARADOXICAL REACTION IN TUBERCULOSIS

15.1 Definition

Paradoxical reaction (PR) is an inflammatory response associated with treatment for TB, has been defined as worsening of the existing disease or appearance of new TB lesions during anti-tuberculosis therapy.

15.2 Pathogenesis

Several pathophysiological mechanisms have been postulated in development of PR in TB. These mechanisms are

1. Rapid killing of bacilli with antibiotics may lead to the release of large amounts of microbial components, which could stimulate an exuberant inflammatory response. Higher baseline numbers of bacilli may potentiate this process and lead to PR.
2. IRIS is due to an outpouring of cytokines produced by T cells that are activated by mycobacterial antigens. PR is result of an exaggerated cell-mediated immune response against damaged or killed mycobacteria by chemotherapy.
3. PR might also result from the recovery from TB-induced immunosuppression which might have led to a local hypersensitive response against massive mycobacterial antigens exposure following ATT.

The worsening could be clinical or radiological in the absence of evidence of disease relapse or the presence of another diagnosis. HIV co-infection is a well-recognized risk factor, usually when concomitant ART is started and is termed the IRIS. This is thought to occur when a functioning immune response returns by the action of ART and worsens TB symptoms during treatment or where undiagnosed TB is 'unmasked' by ART. TB itself is immune-modulatory, and initiation of TB treatment can also reverse immune deregulations. In non-HIV positive people, the reported frequency of PR varies widely, but is lower than that seen in HIV positive people. Some reported research revealed decreased serum hemoglobin, albumin level, lymphocyte count and EPTB were associated with increased risk of PR.

The rate of primary site of disease in extra pulmonary sites was much higher than that in lung regardless of HIV positive or negative.

15.3 The common clinical manifestation

This usually occur from one week to several months after the initiation of ATT. It is more frequent in patients with EPTB or disseminated TB. Symptoms Includes recurring symptoms such as fever, cough and Dyspnea, radiological deterioration, appearance of pleural effusion or ascites, new intracranial TB, either a paradoxical worsening/recurring of pre-existing TB lesions and the progression of lymphadenitis.

Paradoxical response can occur in any system including CNS, respiratory system, skin and soft tissue, lymph node, abdomen, bone and tendon. PR in the respiratory system is often manifested by worsening or new appearance of tuberculous effusion. The newly appeared pulmonary mass is infrequent and may occur in the patients with TBPE. The potential cause of this phenomenon may be that invisible sub pleural PTB underwent transient worsening despite anti-tuberculous medication and they became radiographically evident over time.

This phenomenon is in accordance with the previous report in which PR developed on the same side with primary TB, though contralateral or bilateral lesions can also occur.

15.4 Diagnosis of PR

Several criteria are needed to be taken into consideration for diagnosis of PR, including the initial response to ATTs, paradoxical deterioration of TB-related symptoms and/or radiological findings, exclusion of alternative explanations for clinical deterioration such as drug resistance, poor adherence, drug side effects and other infections.

15.5 Treatment

Currently, there is no guideline regarding management for PR. As many patients have exacerbated symptoms, a combination therapy of corticosteroid and anti-TB is recommended. There are few treatments option available in treatment. All these treatment options are not result of randomized control trail.

1.Steriod treatment: The use of corticosteroid is systemic and short term. Initial dose of corticosteroids is 1 mg /Kg / day and tapering over 4 to 6 weeks duration.

2.Thalidomide: An anti-inflammatory, anti-angiogenic, and immunomodulatory agent, counteracting and reducing TNF-α levels in CSF also seems to be an agent of reasonable benefit. Most studies use a dose of 3–6 mg/kg/day in children or up to 200 mg/day in adults.

Thalidomide often takes few weeks before showing optimum therapeutic effect. Hence, all the studies continued high-dose corticosteroid in cases with TB-IRIS even after starting thalidomide, and combination of these two immunomodulatory agents appear to be safe. Uncertainties remain regarding the optimal doses and duration of thalidomide, whether it should be used in all cases of CNS TB-IRIS, whether the duration should be more for more severe IRIS cases, and the cases with massive tubercular mass lesions including pseudo abscesses.

Most studies stated that the duration of therapy should be guided by the clinical and radiological response; clinical response often precedes radiological response; a radiological marker for cure (in relation to TB abscesses) is loss of signal changes in T2-weighted MRI sequences.

3. Infliximab: Tumor necrosis factor antibody has shown effect of inhibition of cellular immune response to mycobacteria. The experience of the anti-TNF antibody infliximab treatment is effective in treating other types of granulomatous inflammation. PRs involving the central nervous system maybe life threatening. Infliximab treatment has shown to be effective in CNS TB with PR. The optimal timing and duration of anti-TNFα treatment, as well as the value of corticosteroid co-administration, remains unclear. Symptomatic improvement, inflammatory markers (if raised to begin with), and MRI or PET changes may guide treatment duration. A rational approach may be to give 5 mg/kg at 0, 2, and 6 weeks (similar to induction dosing recommended for patients with active psoriatic arthritis), with consideration of additional doses at 10–14 weeks guided by the treatment response.

4. **Vitamin D:** Is recognized as an immune modulator in TB infection. It may mediate PR in ATTs. The course of treatments should be based on the patient condition.

5.Surgical interventions: Include drainage and aspiration are helpful when lesions show as abscess or pleural fluid.

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Chapter 16: TREATMENT OF EXTRAPULMONARY TUBERCULOSIS

16.1 Lymph node TB

A 6-month regimen is recommended for initial treatment of all patients with tuberculous lymphadenitis caused by drug-susceptible organisms. Affected lymph nodes may enlarge while patients are receiving appropriate therapy or after the end of treatment without any evidence of bacteriological relapse. On occasion, new nodes can appear during or after treatment as well. Therapeutic lymph node excision is not indicated except in unusual circumstances. For large lymph nodes that are fluctuant and appear to be about to drain spontaneously, aspiration or incision and drainage appears to be beneficial.

16.2 Pleural TB

A 6-month regimen is recommended for treating pleural TB.

Tuberculous empyema, a chronic, active infection of the pleural space containing a large number of tubercle bacilli, usually occurs when a cavity ruptures into the pleural space. Treatment consists of drainage (often requiring a surgical procedure) and antituberculous chemotherapy. Surgery, when needed, should be undertaken by experienced thoracic surgeons.

16.3 Tuberculous meningitis (TBM)

TBM remains a potentially devastating disease that is associated with a high morbidity and mortality, despite prompt initiation of adequate chemotherapy. Patients presenting with more severe neurologic impairment such as drowsiness, obtundation, or coma have a greater risk of neurologic sequelae and a higher mortality. Chemotherapy should be initiated with INH, Rifampicin, Pyrazinamide and Ethambutol in an initial 2-month phase.

INH and Rifampicin, as well as the aminoglycosides, and the FLQ are available in parenteral forms for patients with altered mental status who may not be able to take oral medications.

After 2 months of four-drug therapy for meningitis caused by susceptible strains, Pyrazinamide and Ethambutol may be discontinued, and INH and Rifampicin continued for an additional 10-12 months. Repeated lumbar punctures should be considered to monitor changes in CSF cell count, glucose, and protein, especially in the early course of therapy.

On the basis of the available data, adjunctive corticosteroid therapy with dexamethasone is

recommended for all patients, particularly those with a decreased level of consciousness, with TBM. The recommended regimen is dexamethasone in an initial dose of 8 mg/day for children weighing less than 25 kg and 12 ug /day for children weighing 25 kg or more and for adults. The initial dose is given for 3 weeks and then decreased gradually during the following 3 weeks.

Dexamethasone dose

No coma or focal signs: 0.3mg/kg/day (max 24mg) withdrawn after 6 weeks

Coma or focal signs+: 0.4mg/kg/day (max 24mg) withdrawn after 6 weeks

16.4 Bone and joint TB

Standard regime for bone and joint TB includes 2 months of induction with INH, Rifampicin, Pyrazinamide, Ethambutol and continuation of INH, Rifampicin, for 7 to 10 months; i.e. a total duration of 9-12 months.

Myelopathy with or without functional impairment most often responds to chemotherapy.

In some circumstances, however, surgery appears to be beneficial and may be indicated. Such situations include failure to respond to chemotherapy with evidence of ongoing infection, the relief of cord compression in patients with persistence or recurrence of neurologic deficits, or instability of the spine.

16.5 Pericardial TB

For patients with pericardial TB, a 6-month regimen is recommended. That is 2 months of induction with INH, Rifampicin, Pyrazinamide, Ethambutol and continuation of INH, Rifampicin, for 4 months. Corticosteroids are recommended as adjunctive therapy for tuberculous pericarditis during the first 11 weeks of ATT.

Based on studies, it is recommended that daily adjunctive prednisolone or prednisone treatment be given to adults and children with tuberculous pericarditis. For adults the prednisone dose is 60 mg/day (or the equivalent dose of prednisolone) given for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks, and finally 5 mg/day for week 11 (the final week). Children should be treated with doses proportionate to their weight, beginning with about 1 mg/kg body weight and decreasing the dose as described for adults.

16.6 Pleural TB

A 6-month regimen is recommended for treating pleural TB. INH, Rifampicin, Pyrazinamide, Ethambutol for 2 months and continuation of INH and Rifampicin for 4 months.

The surgical drainage is indicated, in a case of moderate to large effusion for symptom relief and to minimize chronic complications like pleural thickening, adhesions and restriction to lung expansion, particularly in paediatric age group.

Tuberculous empyema, a chronic, active infection of the pleural space containing a large number of tubercle bacilli, usually occurs when a cavity ruptures into the pleural space. Treatment consists of drainage (often requiring a surgical procedure) and antituberculous chemotherapy. Surgery, when needed, should be undertaken by experienced thoracic surgeons.

16.7 Tuberculous meningitis (TBM)

Treatment regime includes 2 months of induction with INH, Rifampicin, Pyrazinamide, Ethambutol and continuation of INH, Rifampicin, for 10 months.

It is recommended that all patients with TB meningitis receive adjunctive corticosteroids regardless of disease severity at presentation.

Adults (>14 years) should start treatment with prednisolone 20-40 mg if on rifampicin and 10-20 mg if not on rifampicin (equivalent doses of dexamethasone can be given as an alternative), as a reducing course over 6-8 weeks.

Children (<14 years) should be given prednisolone 1-2 mg/kg/24 hr (maximum 40 mg per day or equivalent dose dexamethasone) for 4 weeks, followed by a reducing course over 4 weeks.

16.8 Disseminated TB

This includes generalized multiorgan involvement due to blood borne spread. Disseminated TB with Miliary TB with meningeal involvement may require prolonged treatment (up to 12 months). Early treatment of patients with suspected miliary TB decreases the likelihood of mortality and improves outcome.

Surgical treatment is rarely necessary. Occasionally, a ventriculo-atrial shunt is indicated for hydrocephalus. Multi-disciplinary team may be required in the management.

Adequate attention to nutrition is important. Many patients with miliary TB are debilitated by the disease, and malnutrition can contribute to a weakened immune system.

Once several weeks of effective therapy is given, patient experiences significant clinical improvement. Directly observed therapy is optimal for assuring compliance and preventing relapse.

Paradoxical enlargement of the lymph nodes or intracerebral tuberculomas during adequate treatment may require steroids. Hydrocephalus may require neurosurgical decompression.

Early empirical therapy for suspected miliary TB is prudent. A delay of even 1-8 days contributes to a high mortality rate. Steroids are warranted for hypotension due to presumed adrenal insufficiency after an Adreno corticotropic hormone (ACTH) stimulation test.

For susceptible organisms, the treatment period is I year.

16.9 Genitourinary TB

Renal TB is treated primarily with medical therapy and a 6-month regimen is recommended. That is 2 months of induction with INH, Rifampicin, Pyrazinamide, Ethambutol and continuation of INH, Rifampicin, for 4 months.

If ureteral obstruction occurs, procedures to relieve the obstruction are indicated. In cases of hydronephrosis and progressive renal insufficiency due to obstruction, renal drainage by stenting or nephrostomy is recommended. Nephrectomy is not usually indicated for the treatment of uncomplicated renal TB but should be considered when there is a nonfunctioning or poorly functioning kidney, particularly if hypertension or continuous flank pain is present. TB of either the female or male genital tract responds well to standard chemotherapy, and surgery is needed only for residual large tubo-ovarian abscesses.

A positive urine culture for *M. tuberculosis* occurs relatively commonly as an incidental finding among patients with pulmonary or disseminated disease, especially those with HIV infection. The positive culture may occur in the absence of any abnormalities on urinalysis and does not necessarily represent genitourinary tract involvement.

16.10 Abdominal TB

A 6-month regimen is recommended for patients with peritoneal or intestinal TB. That is 2 months of induction with INH, Rifampicin, Pyrazinamide, Ethambutol and continuation of INH, Rifampicin, for 4 months.

16.11 Other sites of involvement

TB can involve any organ or tissue. In treating TB in sites other than those mentioned, the basic principles of therapy apply, but experts should be consulted for specific advice concerning individual patients.

Chapter 17: CONTACT SCREENING IN EPTB

According to the national policy, contacts of all TB patients have to be traced. Though not infectious, in EPTB patients also contact tracing has to be carried out routinely.

The purpose of contact tracing is to identify the index case from whom the EPTB patient got the infection.

If diagnosed with active TB, such individuals are treated with ATT.

Investigating for TB infection for TB preventive therapy is not recommended for close contacts of EPTB patients. TB preventive therapy is recommended only for close contacts of Pulmonary TB patients.

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