Extrapulmonary Tuberculosis—An Update on the Treatment and Drug Resistance

Davood Yadegarynia

Professor of Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences

Goal of TB Treatment

The goal of Tuberculosis treatment are:

- To decrease case fatality and morbidity by ensuring replace free cure
- To minimize and prevent development of drug resistance
- To render patient non-infectious, break the chain of transmission and to decrease the pool of infection

Case Definitions:

1-Microbiologically confirmed TB Case refers to a presumptive TB patient with biological specimen positive for acid fast bacilli, or positive for Mycobacterium tuberculosis on culture, or positive for tuberculosis through Quality Assured Rapid Diagnostic molecular test.

2- **Clinically diagnosed TB case** refers to a presumptive TB patient who is not microbiologically confirmed, but has been diagnosed with active TB by a clinician on the basis of X-ray abnormalities, histopathology or clinical signs with a decision to treat the patient with a full course of Anti-TB treatment.

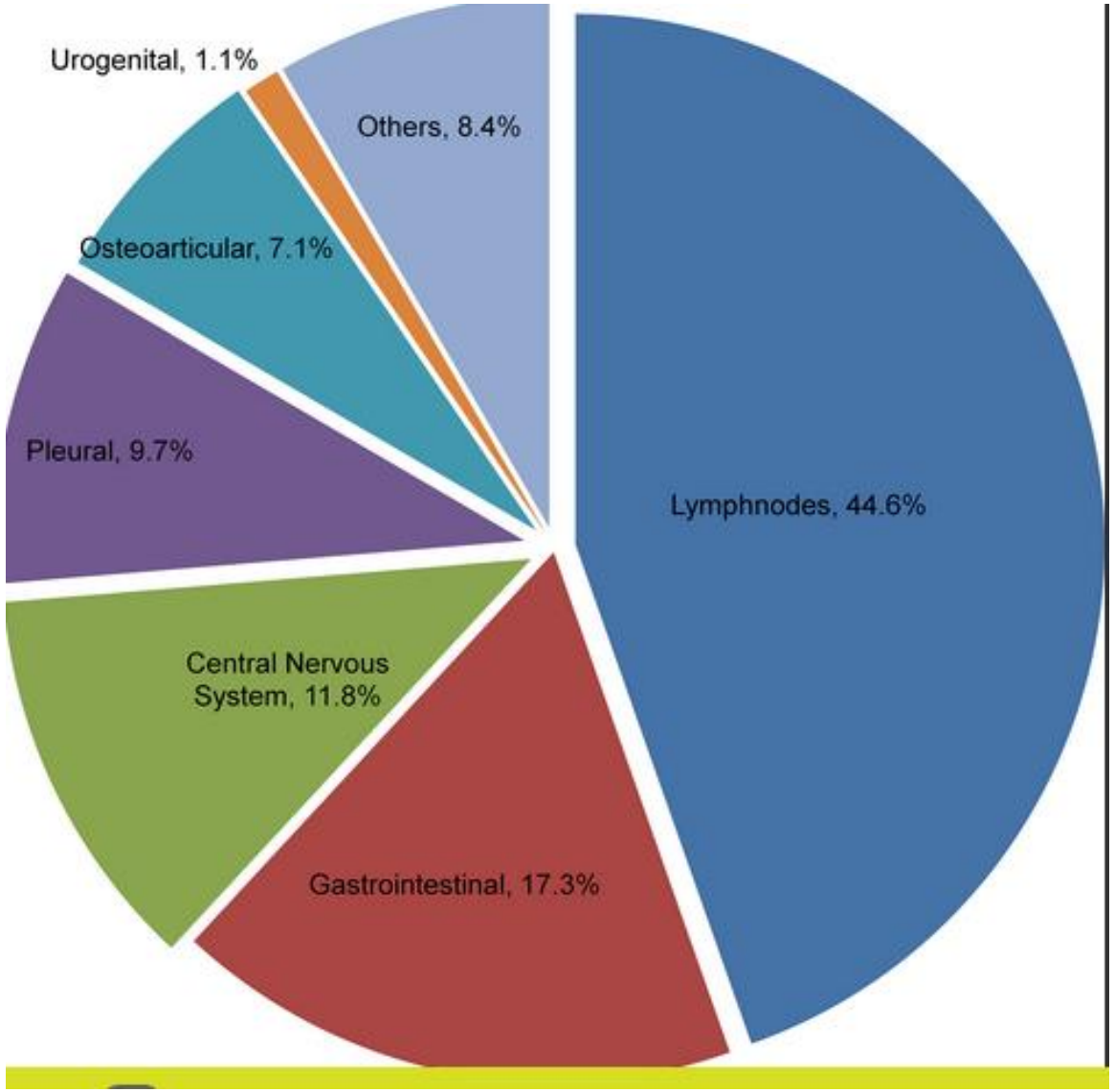
Classification based on anatomical site of disease

A) **Pulmonary Tuberculosis (PTB)** refers to any microbiologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the trachea-bronchial tee.

B) **Extra pulmonary Tuberculosis (EPTB)** refers to any microbiologically confirmed or clinically diagnosed case of TB involving organs other than the lungs such as pleura, lymph nodes, genitourinary tract, joint and bones, meninges of the brain etc.

Classification based on drug resistance

- **A. Mono-Resistance (MR):** A TB patient, whose biological specimen is resistant to one first- line anti-TB drug only.
- **B. Poly – Drug Resistance (PDR):** A TB patient, whose biological specimen is resistant to more than one first-line anti –TB drug , other than both INH and Rifampicin.
- **C) Multi Drug Resistance (MDR):** A TB patient, whose biological specimen is resistant to both isoniazid and Rifampicin with or without resistance to other first line drugs, based on the results from a quality assured laboratory.
- **Rifampicin Resistance (RR):** Resistance to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs excluding INH. Patients, who have any Rifampicin Resistance , should also be managed as if they are an MDR TB case.
- **D) Extensive Drug Resistance (XDR):** A MDR TB case whose biological specimen is additionally resistant to a fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin) and a second-line injectable anti TB drug (kanamycin, amikacin, or capreomycin) from a quality assured laboratory.



Exploring the Sociodemographic and Clinical Features of Extrapulmonary Tuberculosis in Saudi Arabia

Treatment outcome of extrapulmonary tuberculosis under Revised National Tuberculosis Control Programme

Results: Of the total **2219** patients studied, there were more males in age group 15–45. The commonest sites of EPTB were lymph node (34.4%) and pleural effusion (25.2%) followed by abdominal (12.8%) and central nervous system (CNS) (9.4%). Lymph node involvement was more common in females (58%) and pleural effusion in males (70%).

Treatment outcome of extrapulmonary tuberculosis under Revised National Tuberculosis Control Programme

Overall treatment completion rate was 84% in EPTB patients.

Treatment completion was 86% in HIV negative EPTB patients compared to 66% in HIV positive patients.

*Treatment outcome of EPTB was **poor** in HIV infected patients and those with CNS tuberculosis.

Drug resistance among extrapulmonary TB patients: Six years experience from a supranational reference laboratory

Between 2005 and 2012, of the 1295 extrapulmonary specimens, 189 grew *M. tuberculosis*, 37 (19%) cases were multidrug resistant (MDR) while one was extensively drug resistant (XDR).

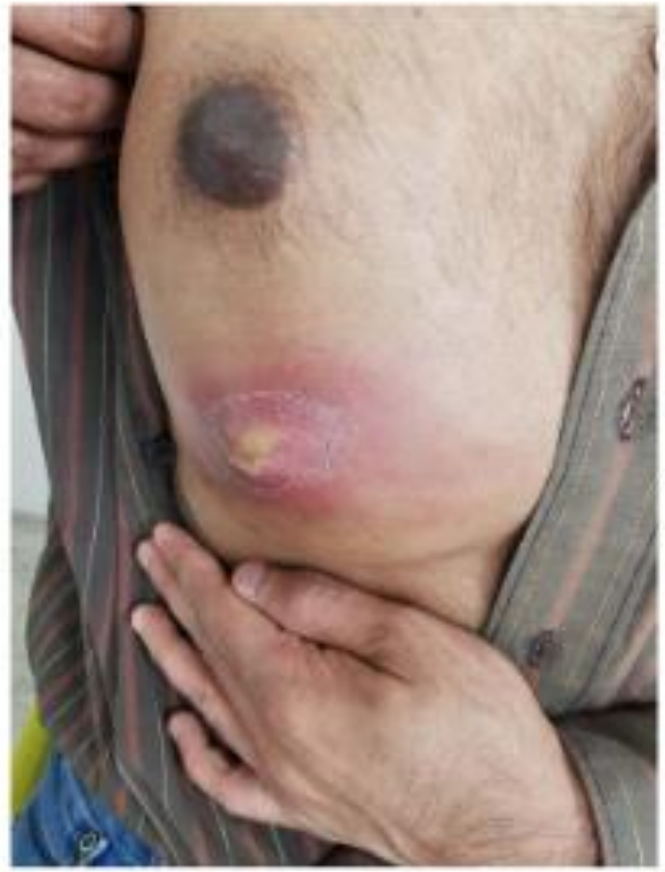
According to the World Health Organization(WHO) global tuberculosis report in 2016, there were 10.4 million incident tuberculosis (TB) cases world wide in 2016.

- Of all new TB cases notified, 15% were reported to be extra-pulmonary TB (EPTB), with the proportion rising to 50% in persons co-infected with TB and the human immunodeficiency virus (HIV).
- EPTB is a paucibacillary disease that requires strong clinical suspicion to be diagnosed.
- The major challenge in EPTB is a relative lack of accessibility to obtain adequate diagnostic specimens from sites such as the nervous system, bones and joints, or eyes.

Extrapulmonary tuberculosis presentation in the form of a chest wall abscess with no pulmonary involvement: a case report

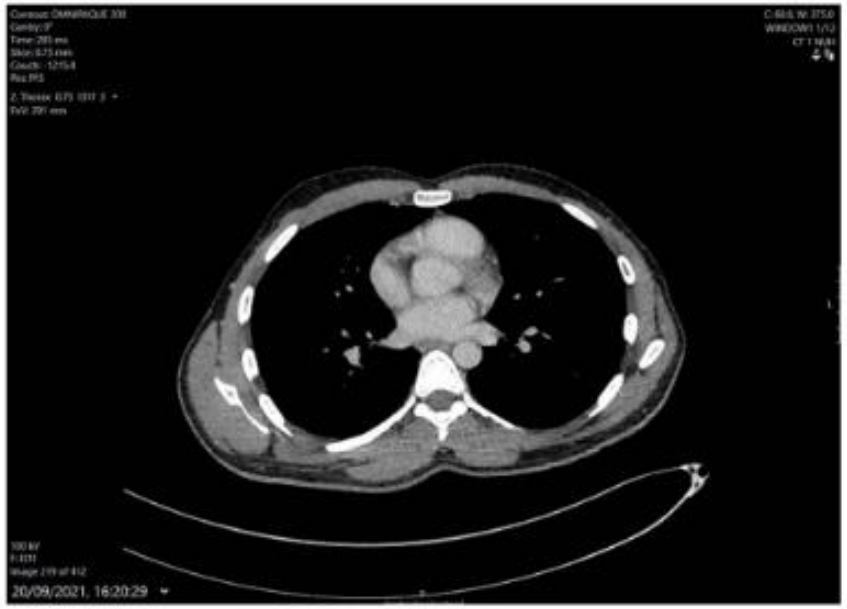
CASE REPORT

A 31-year-old healthy male presented as a general surgical emergency to a tertiary care facility with a 3-monthhistory of a mass on the right side of his chest. It had progressively increased in size and become painful and erythematous days prior to his presentation. He reported no fevers, shortness of breath, cough, night sweats or weight loss. On examination, it was thought to be a suppurative chest wall abscess.



The chest wall abscess at time of presentation.

The PCR and histology results were both positive for TB. Cultures grew a fully sensitive Mycobacterium tuberculosis bacilli. He was seen in ID clinic and commenced on anti-tubercular treatment. Initially, he had 2-month intensive therapy of Rifampin, Isoniazid, Ethambutol and Pyrazinamide. The Pyrazinamide was stopped at 6 weeks due to issues with arthralgia. For maintenance therapy he continued for a total 7 months of Rifampin and Isoniazid due to the short course of Pyrazinamide. He had a repeat CT thorax after completing treatment, which showed resolution of the abscess and infection with no evidence of osteomyelitis



CT Thorax after completing 9 months of medical treatment and surgical debridement of abscess. Shows complete resolution of chest wall mass and intact bony structure underneath.

Extra pulmonary Tuberculosis

Patients with FUO	Retroperitoneal Abscess
Fistulated cervical lymphadenitis	Chronic skin fistula
Chronic meningitis	Chronic monoarthritis
pericarditis	Lower thoracic spondylitis
Fever and Ascites	Chronic pleural effusion
Intermitant hamaturia	Polyserositis
Sterile pyuria	Unexplain uveitis
Bedding epididymitis	Chronic abscess
Chronic diarrhea with fever	Erythema nodosum
Constructive pericarditis	Walking Meningitis

Introduction

- The burden of EPTB is high, ranging from 15–20% of all TB cases in HIV-negative patients.
- While in HIV-positive people it accounts for 40–50% of new TB cases.
- Tuberculous lymphadenitis is among the most frequent presentations of extrapulmonary tuberculosis (TB).

Pathogenesis

- Tuberculous lymphadenitis is considered a local manifestation of the systemic disease, whereas lymphadenitis due to nontuberculous Mycobacteria is truly a localized disease.
- TB lymphadenitis may occur due to:
  - Reactivation of healed focus involved during primary infection
  - Progressive primary tuberculosis i.e. spread from lung into mediastinal lymph node
  - Spread from tonsil and
  - Hematogenous spread due to miliary TB

- Tuberculous lymphadenitis most frequently involves the cervical lymph nodes followed in frequency by mediastinal, axillary, mesenteric, hepatic portal, perihepatic, and inguinal lymph nodes.

Clinical presentaion

- Tb cervical lymphadenitis tends to occur more often in female and presents in young adults.
- Slowly enlarging lymph nodes and may otherwise be asymptomatic.
- Some patients my present with fever ,weight loss, fatigue and night sweats.
- Cough is prominent symptom in mediastinal lymphadenopathy.

Stages of TB lymphadenitis.

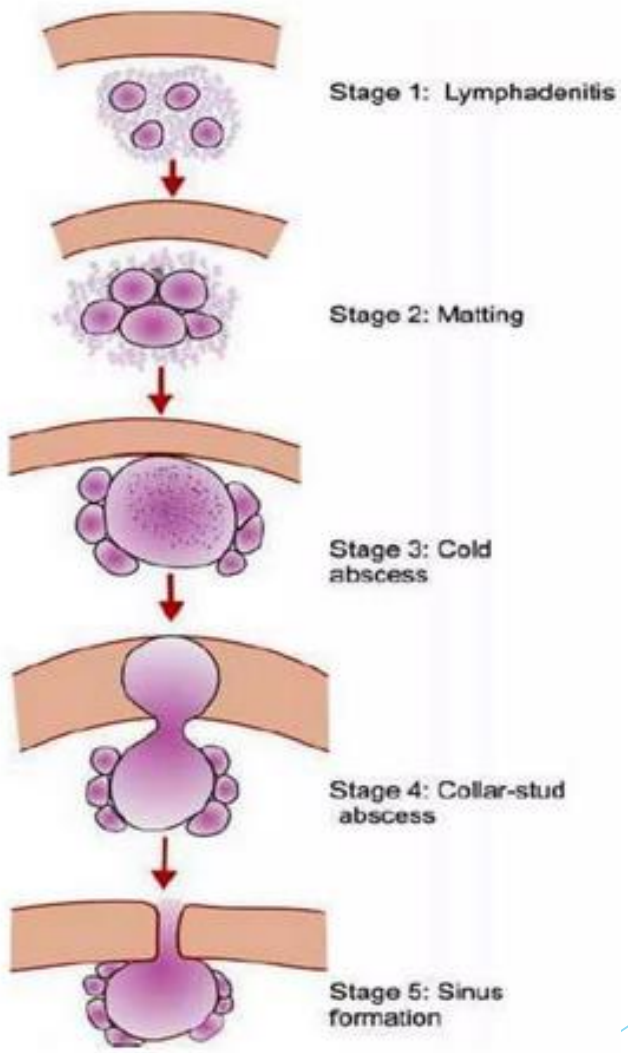
Stage 1 -Enlarged, firm, mobile, discrete nodes.

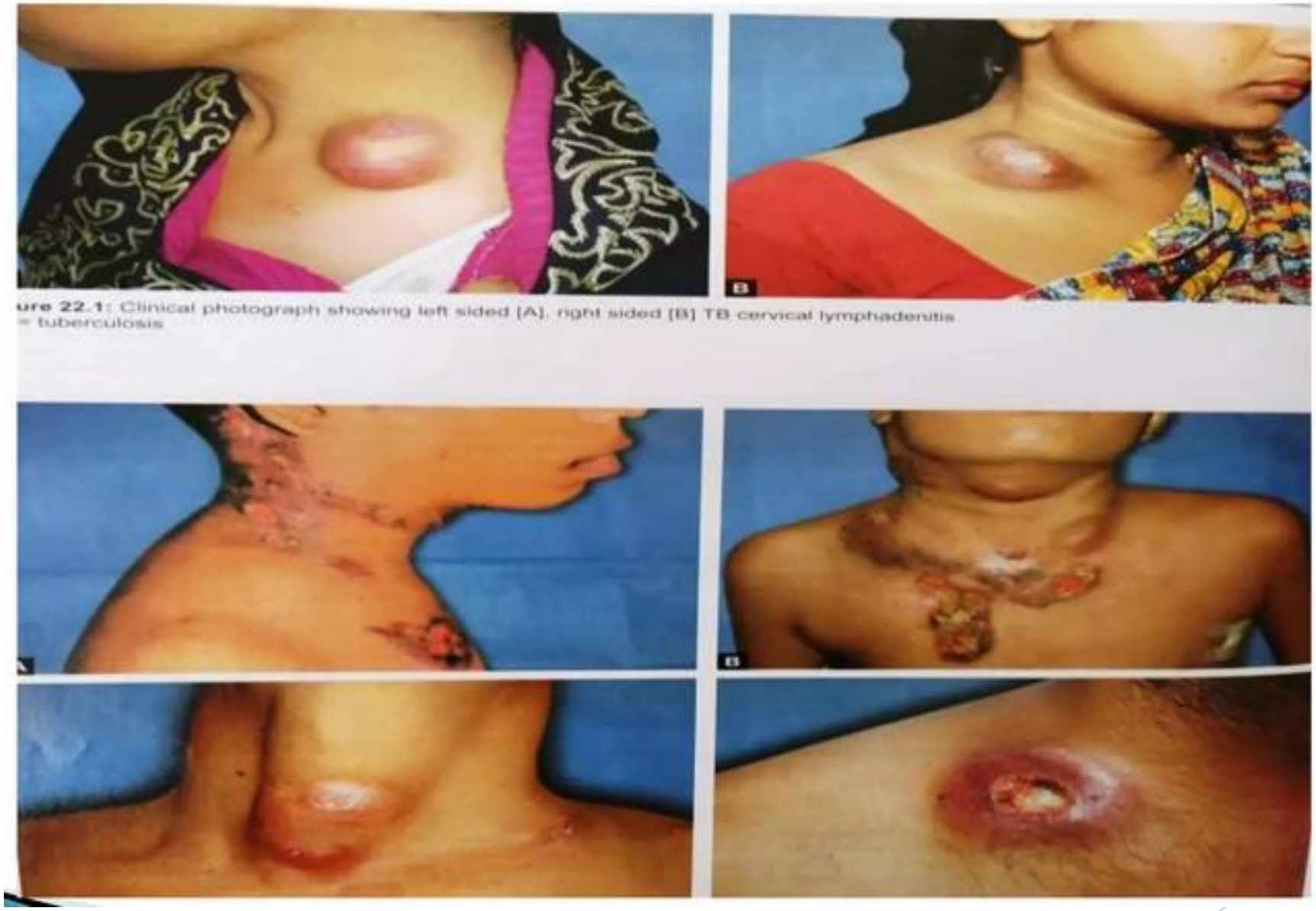
Stage 2- Large rubbery nodes fixed to surrounding tissue

Stage 3- Central softening abscess.

Stage 4-Collar stud formation.

Stage 5-Sinus tract formation. Typical TB sinus has thin, bluish, undermined edges with scanty watery discharge





ure 22.1: Clinical photograph showing left sided [A], right sided [B] TB cervical lymphadenitis
= tuberculosis

Differential diagnosis

- Reactive lymphadenitis, (secondary to viral, bacterial infections)
- Tuberculosis
- Lymphomas
- lymphadenopathy of NTM
- Generalised lymphadenopathy of HIV
- Sarcoidosis
- Secondary carcinomas
- Uncommon causes like fungal diseases, toxoplasmosis

- Multiplicity, matting and caseation are the three features which helps in the diagnosis of TB lymphadenitis.

Patients who should be investigated for LNTB

Presumptive peripheral LNTB

- Patients with enlarged lymph nodes (over 1 cm across) in the neck, armpit or groin.
- And / or with symptoms of
  - fever,
  - weight loss,
  - night sweats and
  - cough

Presumptive mediastinal LNTB

- Patients presented with cough, fever, shortness of breath, weight loss or night sweats.
- And hilar widening on chest X-ray and/or mediastinal lymphadenopathy on chest CT in the absence of evidence of active pulmonary TB.

Presumptive abdominal LNTB

- Patients with dull or colicky abdominal pain, abdominal distension, weight loss, night sweats or fever, and
- Evidence of abdominal lymphadenopathy on abdominal ultrasound scan, CT or MR

Diagnosis

- chest X-ray and HIV test should be done in all patients presenting with symptoms consistent with LNTB, to seek for active or previous pulmonary TB.

- EPTB is associated with HIV infection. All patients should be offered integrated counseling and testing.

Fine needle aspiration cytology (FNAC)

- should be done in all patients.
- Send specimen for:
  - Microscopy and culture for Mtb with drug susceptibility testing;
  - Cytology
  - Xpert MTB/RIF test;

Excision biopsy

- In selected- If FNAC has been inconclusive, or where malignancy is suspected.

- Send specimen for:

1.In normal saline

  - Xpert MTB/RIF test;
  - Microscopy and culture for Mtb with drug susceptibility testing;

2. In formalin

  - histopathology

Ultrasound or CT scans of chest and abdomen

- Selected
- Indicated when diagnosis is not clear, and

- In HIV positive people Finding abdominal lymphadenopathy should prompt biopsy to rule out lymphoma as a differential diagnosis.

- Lymphadenopathy in abdominal tuberculosis usually occurs in mesenteric, peri-pancreatic, periportal, and para-aortic groups of lymph nodes. The distribution reflects the lymphatic drainage of sites in the small bowel and liver that have been seeded haematogenously.

- The nodes may be seen as conglomerate masses and/or as scattered enlarged nodes with hypoechoic or anechoic centres because of necrosis.

- The involvement of retroperitoneal nodes and lesions not confined to one anatomic area of drainage are more suggestive of lymphoma.

- A thickening of the small bowel mesentery of 15 mm or more and an increase in mesenteric echogenicity combined with mesenteric lymphadenopathy has been reported as the characteristic sonographic feature of early abdominal tuberculosis.(@)

Recommendations: Diagnosis of EPTB using the Xpert MTB/RIF test

Lymph node TB

- Xpert MTB/RIF should be used as an additional test to conventional smear microscopy, culture and cytology in fine-needle aspiration cytology (FNAC) specimens.

(Strong recommendation, low quality evidence for sensitivity estimate, high quality evidence for specificity estimate.)

- Pooled sensitivity and specificity against culture are 83.1% and 93.6% respectively.

Diagnostic definitions

Bacteriologically confirmed LNTB case

A patient with symptoms and signs of LNTB and has at least one of the following:

- Positive microscopy for AFB on examination of lymph node fluid or tissue
- Positive culture of Mtb from lymph node fluid or tissue
- Positive validated PCR-based test (such as Xpert MTB/RIF)

Clinically diagnosed LNTB case

A presumptive LNTB patient who undergoes diagnostic testing and has all of:

- Negative microscopy, negative culture and negative PCR based tests.
- No other diagnosis made to explain signs and symptoms.
- Strongly suggestive evidence on other tests, such as radiological findings, histopathological findings, clinical course.

Treatment

First line treatment for adults and children with LNTB-

- 2RHZE/4RHE
- Duration - Six months, standard first-line regimen is recommended for peripheral lymph node TB

- In patients with drug-resistant TB, the treatment must rely upon the recent PMDT (WHO)guidelines which are primarily based on drug sensitivity pattern.

Follow up

Assess response to treatment at 4 months.

- Consider possible treatment failure in patients who have worsened or deteriorated after initial improvement – this requires diagnostic investigation and possibly a change of treatment.

- Deterioration in the first 3 months may be due to paradoxical reaction – this does not require repeat diagnostic tests or change of treatment.

- IRIS –"immune reconstitution inflammatory syndrome", in PLHA patients on ART
- Paradoxical reaction is generally used to describe a clinical worsening of TB disease in HIV – seropositive and negative patients after initiation of ATT.
- Symptomatic management is sufficient in vast majority of cases.
- In case of ARDS, TUBERCULOMA, and pericardial effusion, glucocorticoid therapy is needed for few weeks.
- DST should be done in all case of paradoxical reactions.

Some patients with LNTB have residual lymphadenopathy at the end of treatment.

The largest node is-

- < 1 cm in size - usually do not have continued active TB infection. Reassured the patient.

- > 1 cm in size- classified as partial responders.

  The expert group suggested, these patients should receive an additional 3 months of RHE, followed by a biopsy sent for histology and TB culture in patients who fail to respond to that.

Surgical Management

The indications for surgical management of TB lymphadenitis are:

- Treatment failure: Surgical treatment is beneficial to establish the diagnosis and management of drug-resistant organisms
- Adjuvant treatment for drug sensitive cases: For patients who have discomfort from tense, fluctuant lymph nodes surgical treatment is beneficial
- Paradoxical reaction: In a retrospective review, aspiration, incision, and drainage or excision were associated with a trend toward a shorter duration of paradoxical reactions
- Nontuberculous mycobacteria: In children with NTM lymph node removal has been associated with better outcomes

Difficulties In Management

- Appearance of freshly involved nodes
- Enlargement of the existing nodes
- Development of fluctuation
- Appearance of sinus tracts
- Residual lymphadenopathy after completion of treatment
- Relapses.

There are three essential objectives in TB treatment:

(1) To rapidly decrease the number of TB bacilli in order to reduce morbidity

and prevent patient death as well as decrease the capacity for infection of other people;

(2) To prevent the development or worsening of resistant TB;

(3) To prevent relapses after completing treatment.

it is very important to combine multiple drugs, especially drugs with bactericidal capacity that rapidly reduce bacilli reproduction. **The antituberculosis drugs with the greatest bactericidal capacity are H and FQs**. Tuberculous bacilli continuously undergo spontaneous mutations which may create resistance to a certain antituberculosis drug. If a clone is resistant to a specific drug, it will have a relative advantage over susceptible strains against this single drug, hence the importance of combining several drugs. **When the bacillary load is higher, there is a greater risk of resistance developing; therefore, more drugs should be combined in the intensive phase of treatment.**

Objective 3 should be achieved by prolonging treatment over time and using drugs with a **sterilising effect that are capable of eliminating persistent bacilli**, which seem to restrict their metabolic activity and which cause the relapses that occur following antituberculosis treatment. The drug which plays the most important role in this regard and has demonstrated the **greatest efficacy when preventing relapses is R**.

Rapid molecular tests should be used for the resistance study at least **in patients who are at higher risk of having resistant TB**: **prior treatment of TB**, **especially if there has been poor adherence**; **contact with patients with resistant TB**; and **being from countries with a high incidence of MDR-TB (5% or higher).** Knowing which drugs the patient has taken in the past is also extremely important. When a drug has been taken improperly for a month, the possibility that resistance to this drug has developed should be suspected.

Antituberculosis Drugs

Drugs	Route of administration
First-line drugs	
Isoniazid	PO, IV, IM
Rifampicin	PO, IV
Rifabutin	PO
Pyrazinamide	PO
Ethambutol	PO
Second-line drugs	
Levofloxacin	PO, IV
Moxifloxacin	PO
	IV, IM
Amikacin/kanamycin/streptomycin	
Capreomycin	
Ethionamide	PO
Cycloserine	PO
Linezolid	PO, IV
Clofazimine	PO
Para-aminosalicylic acid (PAS)	PO
Bedaquiline	PO
Delamanid	PO
Imipenem–cilastatin	IV
Meropenem	IV
Amoxicillin–clavulanic acid	PO, IV
Thioacetazone	PO

Drugs recommended for the treatment of multidrug-resistant tuberculosis(WHO,2016).

A. Fluoroquinolones		Levofloxacin Moxifloxacin Gatifloxacin[a]
B. Injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)
C. Other core second-line agents		Ethionamide/Protionamide Cycloserine/Terizidone Linezolid Clofazimine
D. Add-on agents (not part of the core regimen)	D1	Pyrazinamide Ethambutol High-dose isoniazid[b]
	D2	Bedaquiline Delamanid
	D3	Para-aminosalicylic acid (PAS) Imipenem–cilastatin[c] Meropenem[c] Amoxicillin–clavulanic acid[c] Thioacetazone[d]

Situations in which directly observed treatment must be considered.

Factors related to tuberculosis and treatment

- Prior treatment of active tuberculosis or latent infection
- Relapse or treatment failure
- History of treatment non-adherence
- Resistant tuberculosis
- Use of intermittent treatment regimens

Factors related to patient characteristics

- Adolescence
- Poverty
- History of or current drug abuse Chronic alcoholism
- HIV infection
- Psychiatric disorders
- Cognitive impairment, frailty or substantial loss of vision
- Residency in institutions (nursing homes, prisons, etc.)

Proposed treatment regimens for resistance to first-line antituberculosis drugs(except rifampicin).

Resistant	Intensive phase	Continuation phase
Z[a]	R/H/E 2 months	R/H 7 months
E	R/H/Z 2 months	R/H 4 months
H	R/Z/E 2 months	RE 10 months
	R/Z/E/FQ[b] 2 months	R/E/FQ 7 months
	H/R/Z/E[c] 9 months	
H and E	R/Z/FQ 6–9 months	
H and Z	R/E/FQ 9–12 months	
H, E and Z	R/FQ/SLOD/SLID 2–3 months	R/FQ/SLOD 12–18 months in total

Proposed corticosteroid regimen in patients with central nervous system tuberculosis (NICE, 2016)

Doses of dexamethasone per week	Stage	
	1	2–3
1	0.3 mg/kg/day IV	0.4 mg/kg/day IV
2	0.2 mg/kg/day IV	0.3 mg/kg/day IV
3	0.1 mg/kg/day PO	0.2 mg/kg/day IV
4	3 mg/day PO	0.1 mg/kg/day IV
5	2 mg/day PO	4 mg/day PO
6	1 mg/day PO	3 mg/day PO
7	–	2 mg/day PO
8	–	1 mg/day PO

Stage 1: Glasgow score of 15 without neurological signs and patient alert and orientated.
Stage 2: Glasgow score of 11–14 or 15 with neurological signs.
Stage 3: Glasgow score of 3–10 with or without neurological signs.

The exception is tuberculous meningitis:

1. where, in the absence of conclusive clinical trials, most experts and associations recommend prolonging treatment to 12 months (two months of R, H, Z and E to continue with 10 months of R and H).
2. As E crosses the blood–brain barrier poorly even with inflamed meninges, some clinicians have suggested using an FQ instead of E as a fourth drug.
3. Aminoglycosides are also useful in MDR-TB, as they have good penetration during acute inflammation.
4. In patients with MDR-TB, long 18–24-month regimens are recommended.
5. According to expert opinion,1 lumbar puncture should be considered to monitor changes in cell count, glucose and proteins. It should always be accompanied by treatment with corticosteroids, since not using them increases mortality.
6. Surgery should be considered in cases of elevated intracranial pressure or complications such as hydrocephaly or tuberculous brain abscesses

- Patients with spinal TB should be treated with a six-month regimen, unless there is direct spinal cord impairment, in which case the regimen should be prolonged to 12 months.

- Susceptible tuberculous pericarditis should also be treated with a six-month regimen. The use of corticosteroids combined with tuberculosis treatment has always been recommended.

- **The United States guidelines** only recommend this in patients with substantial pericardial effusion, high levels of markers and inflammatory cells or early signs of constriction. Should corticosteroids be needed, it is advisable to start with a dose of 60 mg/day of prednisolone and gradually taper the dose until stopping it altogether in two-three weeks.

Special situations
HIV infection

1. Antiretroviral treatment (ART) raises the possibility of interactions, especially with treatment with R; in some cases, treatment with rifabutin may be valid.
2. The use of intermittent treatment regimens in patients with HIV has a higher rate of relapse as well as development of resistance, especially in more immunosuppressed patients; therefore, these regimens are not recommended.
3. All patients with TB and HIV infection should take ART, regardless of CD4 levels.
4. If the patient was not previously taking ART, it should be started in the first two weeks of tuberculosis treatment in those with a CD4 count <50 cells/l.1,3,4 In patients with a CD4 count ≥50 cells/l, there is a certain amount of disagreement.
5. The 2016 United States guidelines1 recommend starting ART after 8–12 weeks, whereas the 2017 WHO guidelines4 recommend doing so within the first eight weeks.
6. In patients with tuberculous meningitis, ART should not be started in the first eight weeks of TB treatment as it increases mortality.

The elderly

Some experts and associations1,2 recommend not using Z in patients over 65 or 75 years of age as this population is at higher risk of hepatotoxicity. In this case, the continuation phase with H and R should be prolonged to seven months.

Pregnancy and breast-feeding

1. All first-line tuberculostatic drugs cross the placenta but do not seem to have a teratogenic effect. Although R as well as H, Z and E are classified by the FDA as category C drugs, using Z in pregnant patients is much disputed in the United States. The WHO recommends the use of four first-line tuberculostatic drugs in pregnant women.
2. There is no contraindication for breast-feeding if the mother is being treated. Indeed, breast-feeding must be promoted when the patient is no longer contagious. The infant should take pyridoxine (1–2 mg/kg/day) since H is detected in breast milk, albeit in small concentrations

Treatment with TNF-α inhibitors

Expert opinion holds that treatment with TNF- inhibitors should be maintained when active TB is diagnosed, whenever the clinical situation allows it. If it has been suspended, there is no consensus on when it may be resumed. However, small case series have suggested that it is safe to resume treatment with TNF- inhibitors in patients with a good clinical response after completing at least two months of antituberculosis treatment.


با تشکر از حسن توجه شما