CURRENT TRENDS IN TUBERCULOSIS

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TUBERCULOSIS PATHOLOGY

Dr. RG. Wiseman Pinto

Tuberculosis is a common disease encountered in Goa in the Pathology practice.
TB is common in Bangladesh .Congo .Pakistan .Sierra Leone .Uganda and India.
Recent surveys show that the Global burden is 9.6 million cases and 2 million in India.
India has 26 percent of the world's TB cases.
In India there are around 600 deaths per day due to TB
192 cases per 100000 population.
TB is divided into
Pulmonary
Extra pulmonary
Drug sensitive and
Drug resistant.
40 percent of India population harbors TB
But with no disease
When the immunity is low then the patient has the disease
TB is seen in
Children.
Homeless
HIV
IV drug users
Immunosuppressed.
In Goa people of higher socioeconomic status are also affected.
TB.is also classified into
Primary TB
Secondary TB
Miliary TB
Microscopically
There are granulomas composed of caseation epitheloid cells.
Langhans giant cells .lymphocytes .plasma cells histiocytes fibroblasts.
Amyloidosis is an important complication.
There may be cold abscesses.
Ancillary studies for confirmation of TB are important

PEDIATRIC TB

Dr.Vaishali Joshi

TB is preventable & curable disease, still continues to impact lines and development of millions of children worldwide. 35% of Country's population is children <15 years. As per WHO figures, <15 years old contribute to 11% of all TB cases globally. Around 1.1 million children fall ill due to TB infection annually & 2.25 lacks lose their lives.

Though pulmonary TB is the commonest form of TB in children, extra pulmonary TB contributes to a significant proportion of cases as compared to in adults. Especially young infants, malnourished, immuno compromised children are at risk of developing severe forms like miliary TB, TB meningitis etc.

The commonest symptoms of the TB seen in children are fever, cough, night sweats & weight loss or failure to thrive. These symptoms are nonspecific & overlap with several other infections in childhood. Persistent cough or fever of > 2 weeks is a good clinical marker of TB especially if associated with h/o weight loss or contact with active infection case.

Diagnosis of TB in children is often challenging as the disease tends to be pauci bacillary & also difficulty faced in collecting sputum samples in children as they often tend to swallow rather than expectorate.

Presumptive TB is defined as fever & cough of > 2 weeks with weight loss ≥5% in 3 months. Initial recommendation is to do a chest frontal skiagram & not sputum as earlier. If chest x-ray is suggestive, it is considered as "Probable TB" & subjected to microbiological confirmation.

Gastric lavage is preferred over sputum in young infants. Induced sputum or bronchoscopy & lavage are other methods used to obtain sample.

Rapid molecular tests like CBNAAT, LPA are approved by NTEP, which can rapidly identify M.TB.

Intense scientific, clinical research, into diagnosis, treatment, prevention has resulted in several changes in treatment schedules, shorter duration etc. A lot of focus is on prevention, where in TB preventive treatment is given to all household contacts based on IGRA testing.

Despite intense research, pediatric TB still continues to be challenging in terms of diagnosis, treatment.

TREATMENT OF TUBERCULOSIS.

Dr.Sanjivani Keny

- Chemotherapy for Tuberculosis effectively started in the year 1940. Multiple regimens were tried since then. Currently used is the 6 month regimen of four first line drugs which are isoniazid, rifampicin, ethambutol and pyrazinamide.
- In our country it was intermittent chemotherapy with these drugs under Revised National Tuberculosis Control Programme (RNTCP) which is now changed to a daily regimen. Also with the aim of eliminating Tuberculosis from our country by 2025 the programme in year 2020 is renamed as National Tuberculosis Elimination Programme (NTEP) [1]

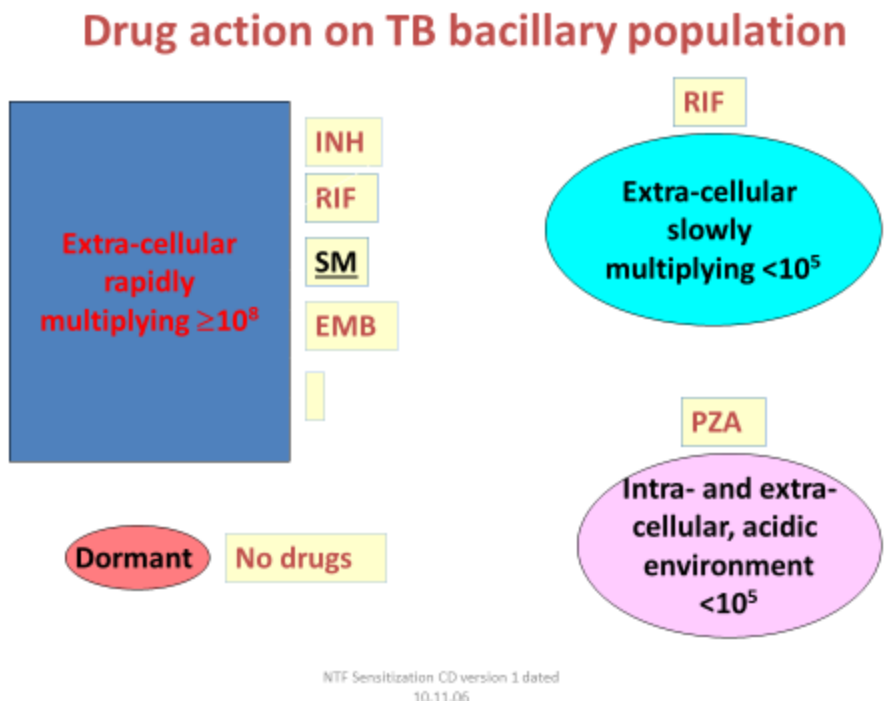
  Objectives of treatment in Tuberculosis are as follows:

1. To render a patient of Tuberculosis non- infectious as early as possible so as to stop transmission of disease in community.
2. To decrease the morbidity and mortality due to illness by initiating treatment early and thus achieving cure from Tuberculosis. And leading to improvement in quality of life.
3. To prevent emergence of Drug Resistance by using multidrug regimen for treatment.
4. To ensure that there are least adverse effects of the drugs used.[2]

Basis of Chemotherapy

There are subpopulations of The Mycobacterium Tuberculosis bacilli which thrive in different environment in TB lesions and multiply either rapidly or in spurts. Some of these bacilli also remain dormant in the body.

Therefore, it is necessary that for treatment, different drugs are used which have unique properties of acting upon these subpopulations of bacilli in different environment or in different modes of multiplication. Regimen for treatment comprises of different drugs which are given together so that all bacillary subpopulations are killed simultaneously and this prevents emergence of drug resistant mutants.[3]



Drugs used in Treatment of Drug Sensitive Tuberculosis

Following drugs are used in treatment of Drug Sensitive Tuberculosis.

1.Isoniazid ((INH/H): This is a bactericidal drug which acts on rapidly multiplying extracellular bacilli.

2. Rifampicin(RIF/R): This is a bactericidal drug which acts on extracellular rapidly multiplying bacilli as well as those multiplying in spurts (semi-dormant bacilli).

3. Ethambutol (ETB/E): This is a bacteriostatic drug which is given to prevent emergence of drug resistant mutants.

4. Pyrazinamide (PZA/Z): This is a bactericidal drug which acts on extracellular as well as intracellular bacilli which grow in acidic environment.

Other reserve drugs used are Injection Streptomycin and Oral Fluoroquinolones. These are used as replacement drugs in event of adverse drug reaction to one of the four frontline drugs or in special situations.[4]

Classification of Tuberculosis

For the purpose of treatment Cases are classified as

1 New Case 2 Previously Treated Case.

New case is one in which patient has never received treatment in the past or has received less than 1 month of treatment.

Previously treated is

1. one who has received more than 1month of treatment and defaulted and then come with microbiologically confirmed TB.

2.one who has completed treatment or has been declared cured and has come with recurrence ie diagnosed again as microbiologically confirmed TB .

3. one who has failed to respond to the ongoing treatment.

4. others who had received treatment in past for more than 1 month are symptomatic , need to be treated but do not fall in any of the above categories.

Another way of classification is

Pulmonary TB (PTB)

Extra Pulmonary TB (EPTB)

Treatment Regimen

Treatment Regimen comprises of Intensive Phase for 2months followed by Continuation Phase for 4 months.

In the Intensive Phase All 4 drugs are given daily ie 2HREZ. 2 number prefixed denotes2 months.

In the Continuation Phase PZA is omitted and only 3 drugs are continued for 4 months ie 4HRE. 4 number prefixed denotes 4 months.

Drugs are given daily and in the form of FDC ie Fixed Dose Combination tablet

Each Adult 4FDC tablet contains all 4 drugs in fixed dose as follows:

INH 75 mgs

RIF 150 mgs

ETB 275 mgs

PZA 400 mgs.

4FDC

4FDC tablets are given in Intensive phase.

Each Adult 3FDC tablet contains 3 drugs in fixed dose as follows

INH 75 mgs

RIF 150 mgs

ETB 275 mgs.

3 FDC tablets are given in continuation phase.

For New Case, Patient will receive 2HREZ followed by 4HRE daily.

2HREZ/4HRE.

For previously treated case, Drug Resistance has to be ruled out by NAAT. Once ruled out patient will receive the same regimen as a new case.

2HREZ/4HRE.

In EPTB like Bone and Skeletal TB and in CNS TB, in addition to 4FDC 5th drug Injection Streptomycin can be given in intensive phase.

Five weight bands are formed under NTEP guidelines.

Number of tablets to be given depends on to which weight band the patient belongs to. The weight bands and number of tablets to be given is depicted in following table.[5]

Adult weight Bands

Daily Dose Schedule for Adults

Weight band	Number of tablets	
	IP	CP
	HRZE	HRE
	75/150/400/275 mg	75/150/275 mg
25-34 kg	2	2
35-49 kg	3	3
50-64 kg	4	4
65-74 kg	5	5
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>75 kg	6	6

NTEP has introduced daily therapy with dispersible tablets in fixed dose combinations (FDC) for children. Younger children get 3-drug FDCs (HRZ) along with 100 mg ethambutol tablets. Older children can also get, in addition, 4-drug FDCs (RHZE) to meet their drug dosages (***Table* III**). Isoniazid and rifampicin are in a ratio of 2:3 and the average dose of isoniazid is around 10 mg/kg/day. These drugs are given free of cost in public sector and the private sector can also access these drugs for free through various partnership schemes that the program offers.

Table III Tuberculosis Drug Formulations and Dosages for Children As per IAP NTEP Guidelines, 2020

Weight band (kg)	Dose from 0-18 y*
4-7	1P + 1E
8-11	2P + 2E
12-15	3P + 3E
16-24	4P + 4E
25-29	3P+3E+1A
30-39	2P+2E+2A

*H-Isoniazid, R-Rifampicin; Z-Pyrazinamide, E-Ethambutol; *number preceding the letter denotes number of pediatric or adult formulations; IAP: Indian Academy of Pediatrics; NTEP: National Tuberculosis Elimination Program; Pediatric formulation (P) H50, R75, Z150 + E 100 (E separate tab); adult formulation (A) H75, R150, Z400, E275; Children (aged 0-18 y) upto the weight of 39 kg should be managed as per this table; children (aged 0-18 y) ³40 kg would be managed as per the various weight bands described for adults.*

Experts now also recommend addition of pyridoxine (10 mg/day) with isoniazid containing regimens because of the risk of peripheral neuropathy due to higher dosages of isoniazid and high prevalence of malnutrition amongst the affected.[6]

Advantages of FDC tablet

FDC tablets ensures that the pill burden is reduced. So better compliance is achieved.

All drugs are taken by the patient and maximum drug levels in blood are achieved at same time. So there is less likelihood of emergence of drug resistant mutants.

Health worker finds it easier to supervise and monitor.

Supplying drugs under NTEP becomes easier.

Assessment during course of treatment

Patient is assessed clinically, radiologically as well as microbiologically during the course of treatment.

Clinical assessment consists of reduction in signs and symptoms, weight gain.

Radiological assessment consists of Chest radiograph, CT scan or MRI depending on site involved, which is compared with one taken before starting treatment.

Microbiological examination is done in Pulmonary TB. Sputum smear microscopy is done at end IP and end CP to see for sputum conversion to negative. If sputum remains positive End IP, repeat sputum NAAT is done to rule out drug resistance. If drug resistance is ruled out, then malabsorption of drugs may be cause of no improvement. In such scenario Therapeutic Drug Monitoring has to be done to see for drug levels achieved in blood. If low one has to increase the dose of that particular drug.

Under NTEP there is no provision for extension of IP and patient has to be switched over to CP at end IP.

If both scenarios are ruled out, then a repeat mid CP sputum microscopic examination has to be done for reassessment as it can be just delayed response to drugs due to coexisting co morbidities like uncontrolled Diabetes Mellitus.

End CP sputum microscopy has to be done to declare the patient cured and End CP culture to rule out recurrence and drug resistance.

If clinically and radiologically there is not total clearance and especially in Extra Pulmonary TB like Bone and Skeletal TB and in CNS TB as per treating physician's judgement CP can be extended further.

At the end of treatment patient is declared as cured if sputum microscopy

report is available as negative. If patient is not getting cough and so not able to give sputum sample, then he is declared as treatment completed. Also in EPTB cases, outcome is given as

treatment completed as no tissue sample is available for reexamination. Both treatment completed and cured cases are counted to calculate treatment success rate.

Treatment in Special Situations

1. Presence of liver cirrhosis in chronic alcoholics, drugs like HRZ can cause hepatotoxicity and have to be replaced with Streptomycin and Fluoroquinolone with ETB.

2. Patients with chronic kidney disease, ETB and PZA have to be given intermittently and not daily depending on kidney function tests.

3. In pregnant females, all drugs HREZ can be given safely.

4. Diabetic patients have to be given Insulin rather than Oral hypoglycemic agents in order to bring DM under control rapidly.[5]

TB and HIV

TB remains one of the commonest opportunistic infection among PLHIV. The treatment of TB remains the same as in other individuals. So the regimen is 2HREZ/4HRE. If patient is already on Antiretroviral (ART) drugs and is tolerating them, one should start Anti TB drugs without delay. However in newly diagnosed patients of TB and HIV infection, Anti TB drugs have to be started first and ART drugs after two weeks if patient has tolerated Anti TB drugs. TB patient with HIV co-infection has to be started on ART treatment irrespective of CD4 count.[7]

Treatment supervision is done by using DOT99 strategy.

Goal: to provide 99% of the benefits of DOTS at a fraction of the cost and inconvenience to patients
DOT 99 strategy ensures better compliance and adherence to Anti TB treatment. Patients are given Anti TB drugs in FDC form at ART center. Monitoring is done as follows.

Patient is given strip of tablets with phone number on back of blister pack. When the patient opens the tablet he has to give missed phone call on that number which is toll free from his registered mobile phone. This gets reflected on dash board as green box which implies adherence to treatment. In case patient has not opened the tablet, box will show red color and indicate noncompliance to treatment.

Corticosteroids in TB

Corticosteroids are strongly recommended in TB Meningitis and in pericardial TB. In HIV positive patients steroids can be given if other infections are ruled out.(index tb). Dose is Injection Dexamethasone 0.4mg/kg body weight in divided doses to be tapered after 2 weeks and stopped after gradually tapering in8weeks.Also oral prednisolone can be given as 1mg/kg body weight.(EPTB Training module)[7]

Immune reconstitution Inflammatory Syndrome (IRIS).

Patients with TB and HIV coinfection after starting both Anti TB and ART drugs may develop sudden worsening of symptoms or new fever due to immune reconstitution. This usually occurs

after 1 month of treatment but sometimes even after 5 days. Steroids for 4 to 6 weeks is treatment for IRIS and dose is 40mgs initially to be tapered and stopped gradually. [2]

Differentiated TB care

This is an approach wherein prompt triage for positive risk factors of newly diagnosed patients is done. The scoring is done based on Body mass index, respiratory rate, oxygen saturation with pulse oximeter, presence of pedal edema, whether patient is able to stand without support or not. Considering the local scenario more risk factors like chronic alcoholism, chronic kidney disease can be added to this. Triage can be easily done by Nursing staff, Medical officer, Pharmacist or by TBHV, ANM. Those found to be triage positive are comprehensively reassessed by treating physician. And depending upon laboratory investigations and clinical examination as well as associated comorbidities a score is assigned. This score helps in deciding whether patient needs admission to a hospital and if so in intensive care unit. By doing this, mortality due to TB even before starting patients on treatment can be reduced.[8]

A GLANCE AT TUBERCULOSIS CONTROL MEASURES

Dr.Savio Rodrigues

Tuberculosis is an age old disease and continues to be a major health problem in India. Like many other health programmes, Government of India stared the National Tuberculosis Programme (NTP) in 1962 for containment of Tuberculosis. Thirty five years later it was noted that this programme did not yield satisfactory results, and at the behest of national and international experts the programme had to be modified in 1997 and was referred to as Revised National Tuberculosis Control Prgramme (RNTCP). Amongst other components RNTCP ensured more stress on diagnosis based on microscopy and directly observed treatment short course(DOTS) therapy. There was establishment of more Designated Microscopy Centers (DMCs) and intermediate reference laboratories (IRLs) for scaling up the diagnostic services

The programme showed encouraging results till 2006, there after drug resistant TB emerged as an additional problem for the programme promotors. In response to this Programatic Management of Drug Resistant TB (PMDT) was introduced in 2007. This programme was aimed at early detection of drug resistant TB, prompt treatment and short term isolation of selected cases in DR-TB care centers especially designed for these patients. By the year 2013 the PMDT was well spread out throughout the length and breadth of the country.

From the year2017, the programme is recast aiming at elimination of TB by the year 2020. With this objective in mind the programme aims at spreading the case detection network, up scaling of diagnostic facilities, creating more centers for detection of first line and second line drug resistance cases, capacity building for surveillance, enrolling private practioners into the programme and preventing emergence of latent TB infection

The 2025 target set for elimination of TB appears to be challenging and has some inherent hurdles as listed below

1. About 35% of adults and 50% of children have latent infection with TB. There is every chance that of one of these person may land up with frank tuberculosis when their immunity goes down or if they suffer from chronic infection. These individuals will then transmit the infection to the community
2. Although TB is a notifiable disease, in many states and general pactionners are encouraged to get involved in the programme and advised to link their TB patients to the

ongoing TB programmes, we do not know how many cases go unreported as there is still some tag of stigmas attached to this disease. Some villages in India has poor net wok connectivity and there may be logistic problems to cover these villages under the programme

3. Some private practioners especially in the rural setting often treat tuberculosis cases with unconventional regimen or treat with suboptimal doses with shorter course duration. This will only promote drug resistance and create additional hindrance to the TB elimination goal. In other cases patient may themselves take a call to stop the treatment, on their own judgment based on "feel good "feeling . We should not forget that 80% of patients go to private practioners for health care and only 20% come under government sector
4. Drug resistance and extended drug resistance in TB like drug resistance in other bacteria cannot if totally surmounted.
5. Finally overcrowding and poor sanitary conditions prevailing in the country generates a good contusive environmental for spread of tuberculosis

TUBERCULOSIS AND HEMATOLOGY

Dr.Mahadev Swamy

Tuberculosis (TB) is highly prevalent chronic devastating disease caused by Mycobacterium tuberculosis present globally especially in the developing countries including India. Despite the advances and the fact that nearly all cases can be cured, TB remains one of the world's biggest threats. In 2014, TB killed 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive).

Reversible peripheral blood abnormalities are commonly associated with pulmonary tuberculosis and these hematological changes act as marker for the diagnosis, prognosis and response to therapy.

TB can cause profound bone marrow and peripheral blood abnormalities by modulating normal hematopoiesis and the disease become more severe when it is co-infected with HIV because of weakened immunity [2].

In pulmonary tuberculosis many hematological and biochemical abnormalities are common and they are valuable aids to diagnosis. A variety of haematological changes have been described in patients with tuberculosis such as anemia, increased erythrocyte sedimentation rate, low serum albumin level and leukocytosis [3].

In active TB cases, anemia and iron deficiency erythropoiesis was observed. A close relationship was found to be exist between severity of tuberculosis and hematological abnormalities. During antituberculous treatment improvements in the hematological values such as, rise in hemoglobin and hematocrit values, were used as indicators reflecting good response to the treatment [4]. Furthermore, fall in values of platelet, white cell and erythrocyte sedimentation rate (ESR) were regarded as markers of good disease control [5].

The comprehensive investigations on hematological changes and abnormalities associated with tuberculosis have been incompletely investigated. There is no comprehensive study assessing the haematological abnormalities in these patients from the Indian subcontinent.

Haemoglobin Concentration:

Anemia was identified in 71% at the time of diagnosis of TB. Of which 67.18% men and 77.7% women with TB had anemia.

Normocytic and normochromic anemia was most common, and was identified in 71.83% anemic patients; and microcytic hypochromic anemia was next common (19.71%). The presence of anemia was associated with age older than 62 years and female sex.

Leukocytes: The WBC count presented variable features. Total leukocytes count was lower than normal in 7.8% and 8.8%, while lymphopenia in 57.8% and 41.2% in male and female patients respectively. Neutrophilia was observed in 64.1% and 58.8%; while neutropenia in 3.1% and 2.9% of the male and female subjects correspondingly.

Thrombocytes:

Although platelet count was found in the normal range in most of the patients, however thrombocytopenia were observed in 14% and 11.8%; while thrombocytosis in 10.9% and 5.9% in male and female patients respectively.

DISCUSSION

Haematological and biochemical abnormalities in pulmonary tuberculosis are common and may be valuable aids in diagnosis. Various studies have shown anemia to be one of the commonest manifestation of TB [7,8]. However, the reported incidences have varied widely from 16–94% of patients with PTB, although, different definitions of anemia were probably applied and the cases were not necessarily freshly diagnosed. Anemia occurred in 71% of our patients, however, TB-associated anemia completely resolved with anti- TB treatment in 64.5% of patients. In addition, the anemia improved considerably in the other patients. All chronic infections including TB can cause anemia [9]. Although a normocytic, normochromic anemia was most common in this study, other types of anemia, including hypochromic microcytic anemia, were not rare. Female sex and old age were risk factors for TB- associated anemia in our data.

In this study of newly diagnosed cases of active TB, we found that ESR was elevated in 87% and normal in 26% of the patients. The mean ESR in pulmonary TB patients was found to be 71.77. In a study, conducted in India, authors concluded that it probably holds true that a lower ESR value in a TB case might be associated with HIV infection in a developing country such as India, and that the higher the ESR value the lower the chance of associated HIV infection [10]. The findings of our study tend to suggest that active TB is associated mostly with very high ESR values (≥ 100 mm/h). In patients with suggestive features of TB but without any other underlying disease affecting the ESR, the baseline ESR may be a valuable diagnostic test to suspect TB in resource poor countries.

Patients with tuberculosis had significant lympho- poenia associated with anaemia, neutrophilia and monocytosis. None of these derangements correlated with radiological extent of lung disease or cutaneous tuberculin reactivity. Lymphocyte counts returned to normal within 2 weeks of initiating chemotherapy in all lymphopoenic patients and normal ranges for all blood counts were restored by 6 months in all the patients studied. In a smear-negative patient, a clinical diagnosis of tuberculosis would be supported by the finding of lymphopoenia, not lymphocytosis. This

finding is in accordance with former study in which increased numbers of neutrophils and lymphocytes in TB patients were reported in Ibadan, Nigeria [11].

Thrombocytopenia and thrombocytosis was also observed in most of the patients in our study, as reported earlier by Olaniyi and Akeuova and Hungund et al [11,12]. Thrombocytosis is assumed to be due to increased thrombopoietic factors as an inflammatory response. Varied mechanisms like drugs immune mechanisms, bone marrow fibrosis and hypersplenism have all been implicated as possible causal factors for thrombocytopenia. Interleukin-6 has also been regarded as potent thrombotic factor released by inflamed cells.

There was elevated level of ESR in all the patients to substantial level whereas Haemoglobin (Hb) was lower in most of the patients presenting anaemic situation. The WBC exhibited varying degree of alteration with neutropenia and lymphopenia. The platelet count was also lower than normal in most of the patients. Some haematological abnormalities are quite common in patients with pulmonary TB and physicians must maintain a high index of suspicion for diagnosis of pulmonary TB in patients with these abnormalities. However, these parameters can be used as indicators in the assessment of response to chemotherapy. In view of the varied haematolo- gical abnormalities observed in patients with tuberculosis in patients of this geographical location. We suggest the differential diagnosis of tuberculosis should be entertained in patients with varied haematological disorders and effective awareness programmes should be launched in rural areas to minimize the chances of spread of the disease.

TB-HIV COLLABORATIVE ACTIVITIES

Dr. U.J. Wanda Viegas

Four pronged strategy between NACP and RNTCP

Prevention

1. Isoniazid Preventive Therapy (IPT)
2. Air-borne Infection Control (AIC)
3. Awareness generation

Early Detection of TB-HIV

1. 100% coverage of PITC in TB patients
2. PITC in Presumptive TB cases
3. Rapid diagnostics for detecting TB and DR-TB in PLHIV
4. ICF activities at all HIV settings: ICTC, ART Centre, LAC and TI settings

Prompt Treatment of TB-HIV

1. Prompt initiation of TB Treatment
2. Early Initiation of ART

Management of special TB-HIV cases

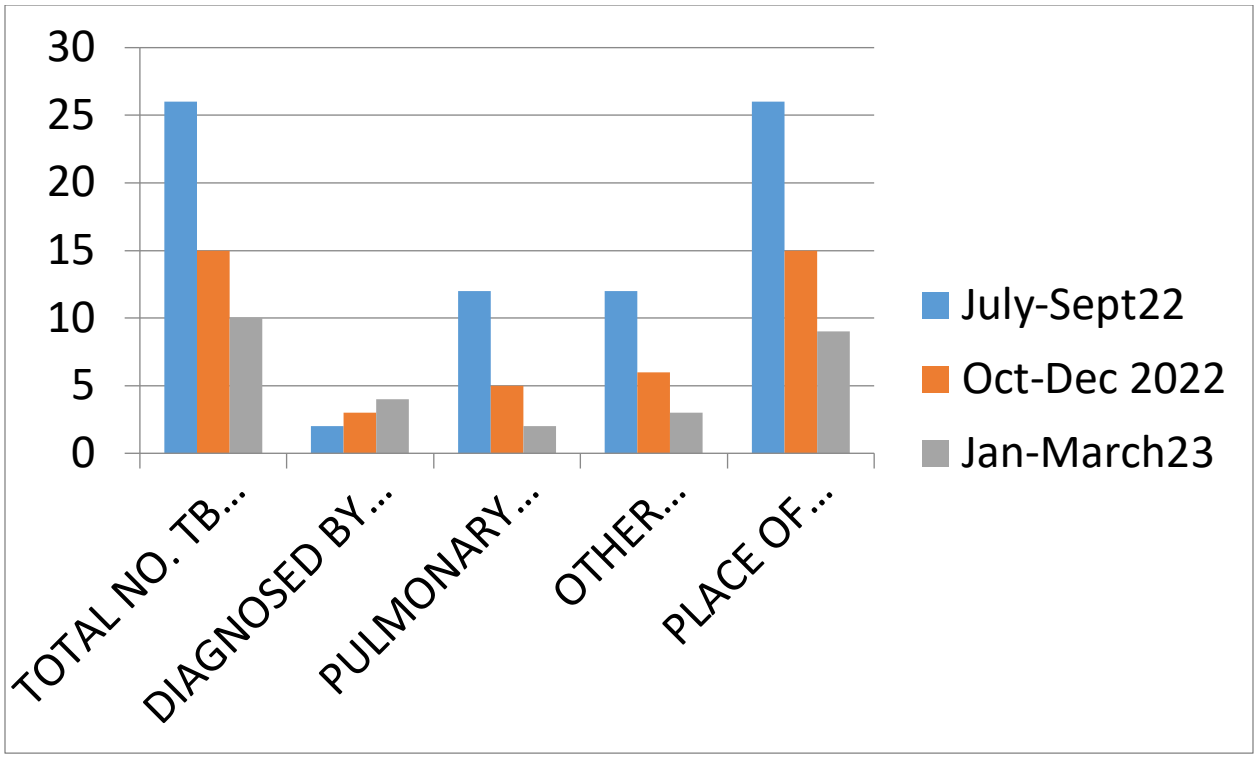
1. TB-HIV patients on PI-based ART
2. TB-HIV in children
3. TB-HIV in pregnant women
4. Drug Resistant TB-HIV

Key Policy Decisions

1. Policy of Provider Initiated Counselling and Testing (PITC) (HIV testing) among presumptive TB patients
2. Intensified case finding activities in HIV care settings
   - Prioritising to offer rapid molecular test Xpert-MTB/Rif (CBNAAT) to all presumptive TB cases among PLHIV for early diagnosis of TB as well as Rifampicin resistance
3. Airborne infection control at ART centres and associated HIV care settings
4. Isoniazid Prevention Therapy (IPT) provision among PLHIV
5. Daily Treatment Regimen with FDC for TB

TB: Common mode of Transmission

- Millions of tubercle bacilli in lungs (mainly in cavities)
- Coughing projects droplets into the air that contain tubercle bacilli
- One cough can release 3,000 droplets
- One sneeze can release tens of thousands of droplets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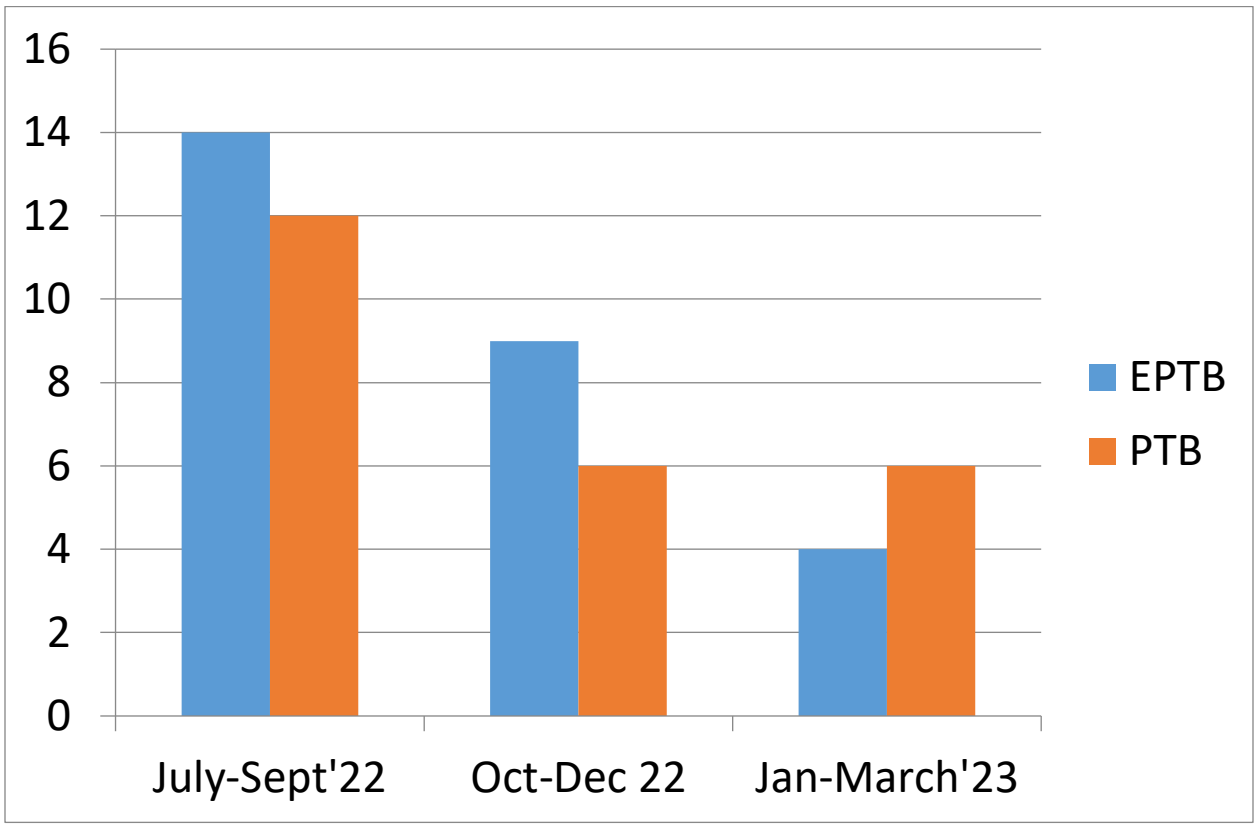
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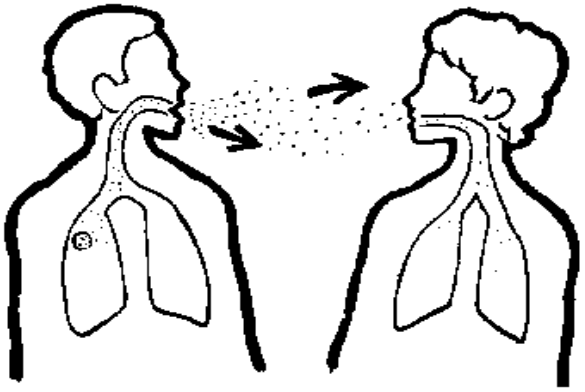
EPTB
PTB

TB: Airborne Transmission

TB bacteria become airborne



A person with active, pulmonary TB releases the TB bacteria into the air

Another person breathes in the air that contains the TB bacteria

TB transmission occurs when a person inhales droplet nuclei with M Tuberculosis and it travels through mouth or nose to reach lung alveoli

4 Symptom Complex for TB screening among PLHIV

Adult

- Current cough
- Fever
- Weight loss
- Night Sweats

Children

- Current cough
- Fever
- Poor weight gain
- Contact with TB case

Factors influencing TB transmission

- Susceptibility
- Infectiousness
- Environment
- Exposure

Clinical factors

- Cough of any duration
- Current cough, fever, night sweats & weight loss in PLHIV
- Resp. Tract infection – involvement of larynx most infectious
- Not covering nose and mouth while coughing
- Inappropriate or inadequate treatment

Standards for TB Care in India

Standard 7: Treatment with first-line regimen

7.1 Treatment of New TB patients:

- The initial phase: H, R, Z, E for two months
- The continuation phase: H, R, E for at least four months

7.2 Extension of Continuation Phase: Extend CP by 3 to 6 months in special situations like Bone & Joint TB, Spinal TB with neurological involvement and neuro- tuberculosis

7.3 Drug Dosages: As per body weight in weight bands

7.4 Bioavailability of Drugs: Ensured for every batch

RNTCP Regimens & Bodyweights of Indian patients

- Current RNTCP regimens for adults based on three weight-bands
  - <30 kg
  - 30-60 kg
  - >60 kg
- Dose of INH is inappropriately high for those in the band of 30-40 kg (~ 45% in our cohort)
- Drug toxicity related to INH in underweight patients is possibly one of the reasons for adverse effects and default

Single vs. FDC Blister Pack

Single-Dose Blister Pack

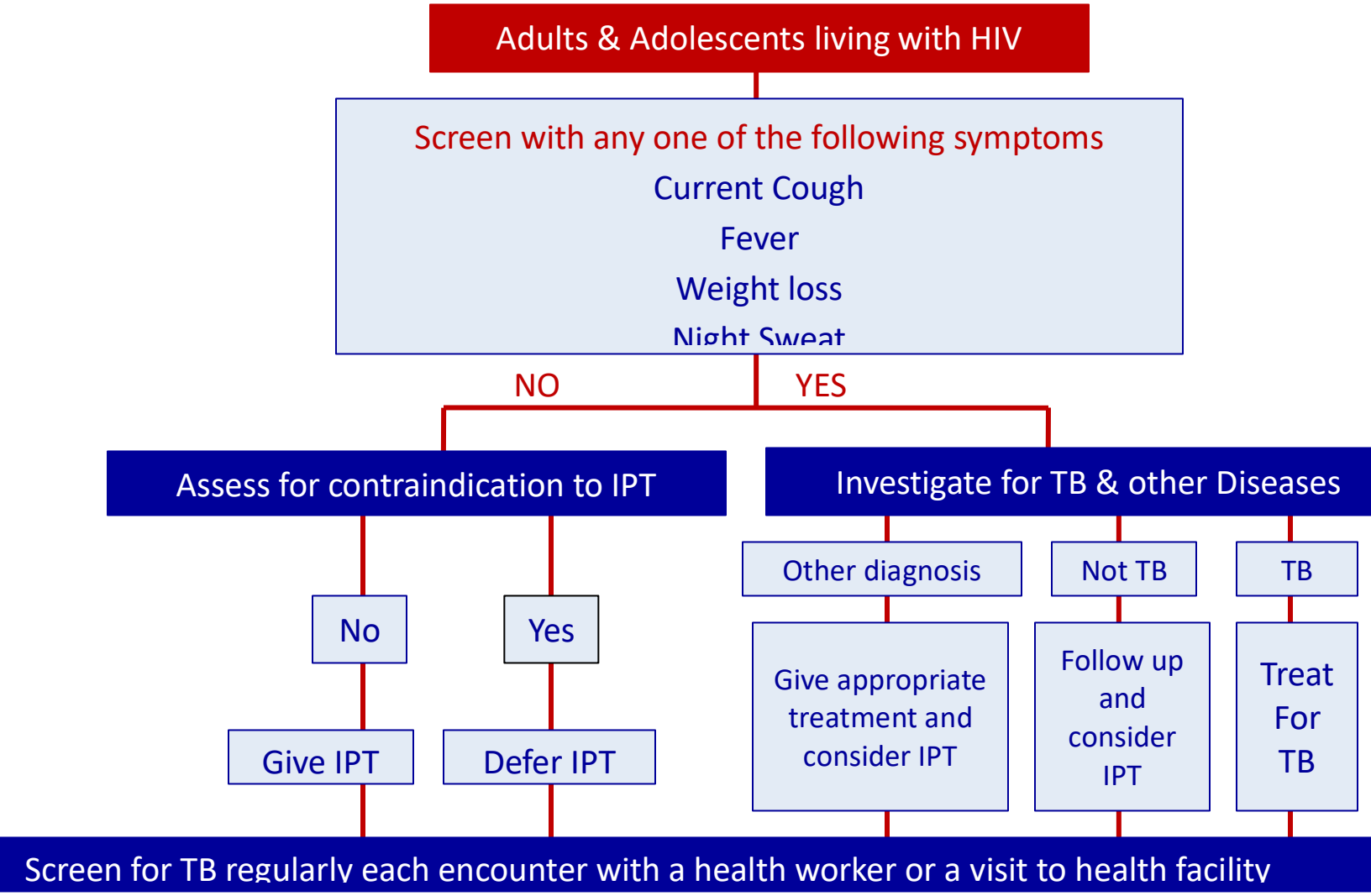
FDC Blister Pack

Anti-TB Drugs used in RNTCP

Regimen I	Regimen II	Regimen IV	Regimen V
Isoniazid	Isoniazid	Kanamycin	Capreomycin
Rifampicin	Rifampicin	Levofloxacin	PAS
Pyrazinamide	Pyrazinamide	Ethionamide	Moxifloxacin
Ethambutol	Ethambutol	Cycloserine	High dose-Isoniazid
	Streptomycin	Pyrazinamide	Clofazimine
		Ethambutol	Inezolid
		PAS*	Amoxyclav
		Capreomycin*	Clarithromycin*
		Moxifloxacin*	Thioacetazone**

Common and rare side effects of Anti-TB drugs

Common (1-10%)	Rare (Less than 1%)
Nausea and vomiting Gastritis Hepatitis Hypersensitivity reactions Cutaneous reactions	Flu like syndrome Peripheral neuropathy Ocular toxicity Joint related side effects Myelosuppression Anaemia Thrombocytopenia Psychosis Seizures



CBNAAT: Evidences and advantages

- Sensitive and Specific
- Increases Case Detection
- Improves quality of rapid TB diagnosis
- Early diagnosis and reduced time taken to Treatment initiation
- Detection of Rifampicin Resistance
- Feasible-minimal bio-safety requirements and training needs; can be housed in non-conventional laboratories

99DOTS

- Medical Officer, ART Counsellors, Staff Nurse and STS/TBHV of nodal TU will provide initial counselling on 99DOTS
- District DR-TB & HIV-TB coordinator is responsible for monitoring patient adherence on 99DOTS, coordinating follow-up with non-adherent patients and recording follow-up actions on 99DOTS website
- Patients showing missed doses under 99DOTS will receive a follow-up action (phone call or house visit)
- The District DR-TB & HIV-TB coordinator will either call patients directly, or will call concerned STS/TBHV to undertake follow-up
- Every follow-up action will be recorded on the website, including reasons identified for patient's non-adherence and steps taken to improve adherence

Promote cough etiquette

- Minimise the potentially infective droplet nuclei
- Display posters on cough etiquette
- Disposable medical masks can be provided free of cost to patients
- Safe disposal of tissue paper, pieces of cloth, masks and of sputum used for covering the mouth to be enforced
- Cough etiquette should be reinforced by all health-care workers when poor cough etiquette is observed

Occupational Health Measures

- Staff receive annual screening evaluations for TB and offered HIV test
- Staff offered treatment, leave and reassignment if HIV-positive
- A log of staff diagnosed with TB is maintained

Natural Ventilation

- Refers to fresh dilution of air that enters and leaves a room though openings such as windows or doors
- Unrestricted openings (i.e. those that cannot be closed) on opposite sides of a room provide the most effective natural ventilation
- Optimized by increasing the window size, opening-up fixed window panes, placing windows on opposing walls, and using a propeller "mixing fans"

CLINICAL DIAGNOSIS OF TUBERCULOSIS

Dr. Swapnil M. Solanki

Introduction

Thought to be one of the oldest human diseases.Reference in the Vedas as "rajayakshma" meaning

Wasting disease. Hippocrates referred to a disease called "pthiasis", a Greek word meaning "to consume". JL Schonlein, Prof of medicine at Zurich coined the Word Tuberculosis from the Latin word "tubercula" Meaning small lump referring to the gross appearance Of granulomas in autopsy specimen. Robert Koch discovered mycobacterium tuberculosis on 24th march in 1882.

He showed it to be the causative agent of tuberculosis and was awarded the Nobel prize in 1905 for the same.

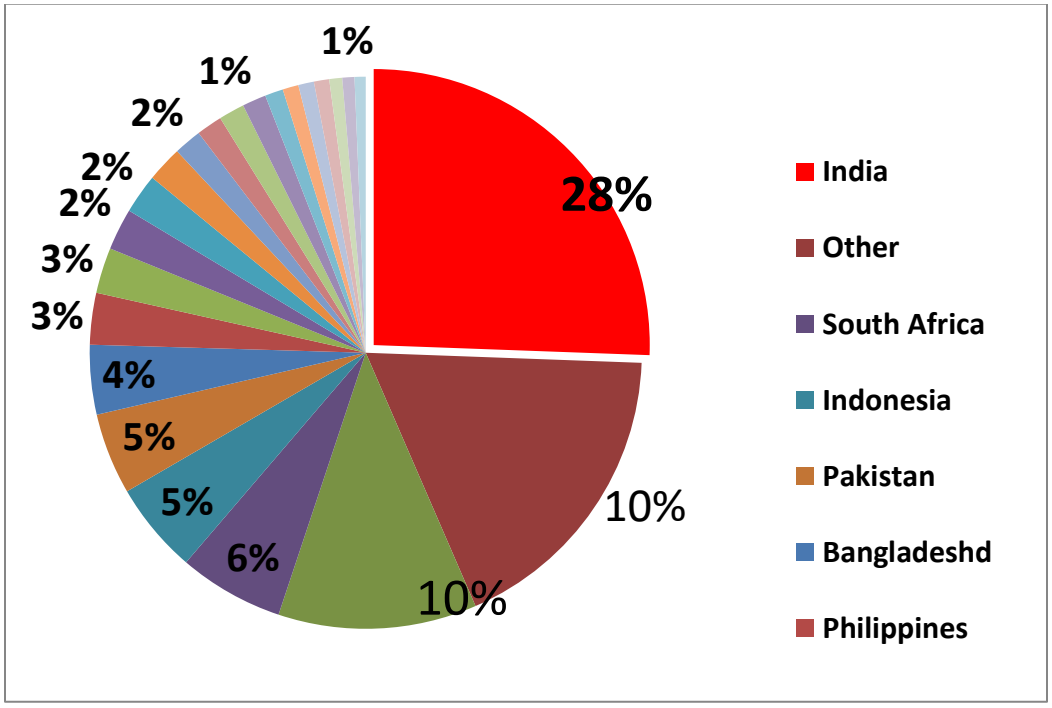
Tuberculosis – infectious disease caused by

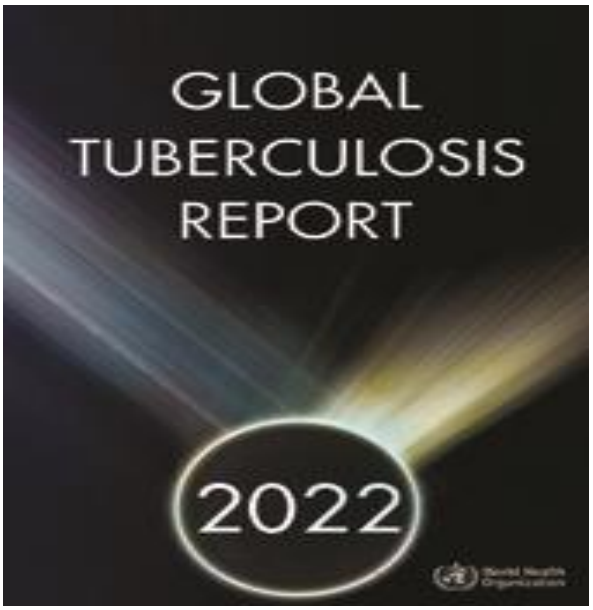
1.Mycobacterium *tuberculosis*

2.Mycobacterium *bovis*

Burden of Tuberculosis

- India has more than a quarter of the Global TB burden.
- Global annual incidence = 10.6 million
- India annual incidence = 2.95 million

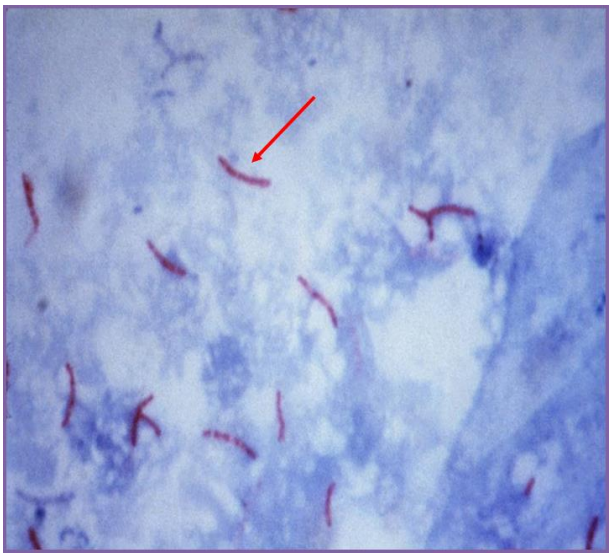




ESTIMATES OF TB BURDEN (2020)	GLOBAL		INDIA		% GLOBAL BURDEN
	NUMBER	RATE (PER 1,00,000 POPULATION)	NUMBER	RATE (PER 1,00,000 POPULATION)	
TB INCIDENCE	1.06 CR	134	29.5 LAKH	210	26%
HIV-POSITIVE TB INCIDENCE	7.03 LAKH	8.9	54,000	3.9	7%
HIV-NEGATIVE TB MORTALITY	13.80 LAKH	17	4.94 LAKH	35	38%
TB MORTALITY	15.67 LAKH	15.6	5.05 LAKH	35	37%
MDR-TB**	4.5LAKH	(5.7)	119,000	(8.5 %)	27%

Characteristics of *M.tuberculosis*

- Slightly curved, rod shaped bacilli
- 0.2 - 0.5 microns in diameter; 2 - 4 microns in length
- Acid fast - resists decolorization with acid/alcohol
- Multiplies slowly (every 18 - 24 hrs)
- Thick lipid cell wall
- Can remain dormant for decades
- Aerobic
- Non-motile



How is TB Transmitted?

- Less frequently transmitted by:
    - Ingestion of *Mycobacterium bovis* found in unpasteurized milk products
    - Laboratory accident

Dynamics of Cough

Large Droplets – fall fast ! Small droplets – hang around... ...slowly evaporate... ...."crystallize" creating a nucleus of infectious material inside...1.0 micron droplet nucleus will eventually fall just 3 m in 24 hrs

- Large droplets – upper airway trapping
- 1-5μ droplet nuclei reach alveoli & cause infection

WALLGRENS TIMETABLE FOR PRIMARY TUBERCULOSIS

Table 56.2 The 'timetable' of primary tuberculosis

Stage	Duration	Features
1	3–8 weeks	The primary complex develops. Conversion to tuberculin positivity occurs
2	About 3 months	Life-threatening forms of disease due to haematogenous dissemination occur, i.e. tuberculous meningitis and miliary tuberculosis
3	3–4 months	Tuberculous pleurisy may be the result of either haematogenous spread or direct spread from an enlarging primary focus
4	Up to 3 years	This stage lasts until the primary complex resolves. More slowly developing extrapulmonary lesions, particularly in the bones and joints, may appear
5	Up to 12 years	Genitourinary tuberculosis may occur as a late manifestation of primary tuberculosis

Latent TB Infection (LTBI)

Person:

- Not ill
- Not contagious
- Normal chest x-ray
- Usually the tuberculin skin test is positive

Germs:

- Sleeping but still alive
- Surrounded (walled off) by body's immune system

RISK FACTORS FOR PROGRESSION

Persons with certain medical conditions such as:

- Diabetes mellitus
- HIV
- Chronic renal failure or on hemodialysis
- Solid organ transplantation/immunosupressive therapy

- Certain types of cancer (e.g., leukemia/lymphomas)/chemotherapy
- Gastrectomy or jejunoileal bypass
- Underweight or malnourished persons
- Silicosis

ENVIRONMENTAL FACTORS

- Persons who live or spend time in certain congregate settings
    - facilities for the elderly
    - jails, prisons
    - shelters for the homeless
    - drug treatment centers
- Overcrowded habitation (housing)
- Health care setting

Pulmonary Tuberculosis

Cough with sputum production

- Any cough that last more than 2 weeks.
- Cough of any duration in a known contact.
- Cough of any duration in a HIV positive patient.
- Cough of any duration in a known case of extrapulmonary TB.
- Cough accompanied by hemoptysis.

Other Symptoms

- Malaise, anorexia, weight loss and fever
- The fever is usually low grade and remittent (appearing late each afternoon and then subsiding)
- Breathlessness
- Hemoptysis
- Pleuritic pain

Clinical signs

- Cachexia

- Pallor
- Febrile/ tachycardic
- Peripheral lymph nodes
- RS: cavernous bronchial BS

  decreased BS

HIV AND TB CO-INFECTION

- HIV is the strongest of all known risk factors for development of TB and is known to affect the Th-1 cell mediated immune responses that are central immune defenses against M.tb.
- At the time of diagnosis of TB in in most patients with HIV have advanced HIV disease with low CD4 + T cell counts and high viral loads or WHO Stage 3 or 4.
- The clinical presentation of HIV-TB is diverse and often atypical depending upon the stage of HIV infection.

Clinical Presentation of TB in early and late HIV infection

FEATURES	EARLY HIV	LATE HIV
Clinical presentation	Often resembles post primary TB	Resembles Primary TB
Sputum smear	Often Positive	Often negative
Radiological appearance	Upper lobe +	Lower Lung field+
	Cavitatory lesions	Cavitation rare
		Intra-thoracic LN-TB
		Diss TB more common
		Pleural/ Pericardial effusions

Definition of presumptive TB

Existing Term RNTCP	Existing RNTCP Definitions	New term RNTCP	New Definitions under RNTCP
Pulmonary TB Suspects	Persons having cough of 2 weeks or more, with or without other symptoms, are referred to as pulmonary TB suspect. They should have 2 sputum samples examined for AFB.	Presumptive TB	Presumptive TB refers to a person with any of the symptoms and signs suggestive of TB including cough >2 weeks, fever > 2 weeks, significant weight loss, haemoptysis, any abnormality in chest radiograph. Note: In addition, contacts of bacteriologically confirmed TB Patients, PLHIV, diabetics, malnourished, cancer patients, patients on immune-suppressants or steroid should be regularly screened for sign and symptoms of TB.

Presumptive Pulmonary TB

Presumptive Pulmonary TB refers to a person with any of the symptoms and signs suggestive of TB including:-

-Cough for > 2 weeks

-Hemoptysis

-Fever >2 weeks

-Significant weight loss

-Any pulmonary abnormality in chest radiograph

Presumptive Extra Pulmonary TB

Presumptive Extra Pulmonary TB refers to the presence of organ specific symptoms and signs like swelling of lymph node, pain and swelling in joints, neck stiffness, disorientation, etc., and/or constitutional symptoms like significant weight loss, persistent fever for ≥ 2 weeks, night sweats.

Case definitions

Microbiologically confirmed TB :

Presumptive TB patient with biological specimen positive for AFB, or positive for MTB on culture, or positive for TB through Quality Assured Rapid Diagnostic molecular test.

Clinically diagnosed TB case:

Presumptive TB patient who is not microbiologically confirmed, but diagnosed with active TB by a clinician on the basis of X-ray, histopathology or clinical signs with a decision to treat the patient with a full course of Anti-TB treatment.

In children, this is based on the presence of abnormalities consistent with TB on radiography, history of exposure to an infectious case, evidence of TB infection (positive TST) & clinical findings suggestive of TB in event of negative or unavailable microbiological results

Pleural TB- NTEP 2023

Figure 1: Pleural TB Flowchart

Diagnostic Algorithm

SUSPECT:

History: Any combination of - acute or chronic onset cough, chest pain, fever (low or high grade), shortness of breath, weight loss, loss of appetite, night sweats

Examination: s/o effusion - stony dull note on percussion, decreased breath sounds

↓

Routine investigations: CBC, LFT, KFTs, PT/INR (rule out contraindication to pleural tap)

Radiography:

Chest x-ray: For **ALL cases** even pregnant females with consent and abdominal shield

Ultrasound: When available, use for guided pleurocentesis

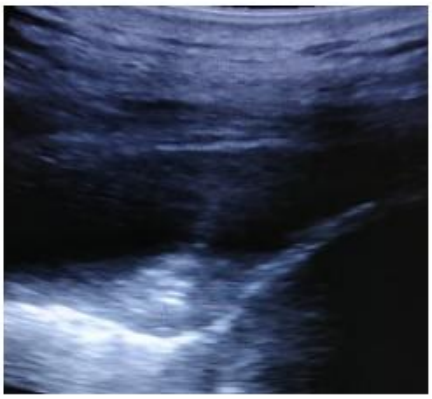
CT: Only if alternate diagnoses like malignancy strongly suspected

Note :AFB, GeneXpert and MGIT liquid culture are not routinely recommended due to resource constraints and low sensitivity , however where available they can be considered

Pleural effusion diagnosed by radiologically

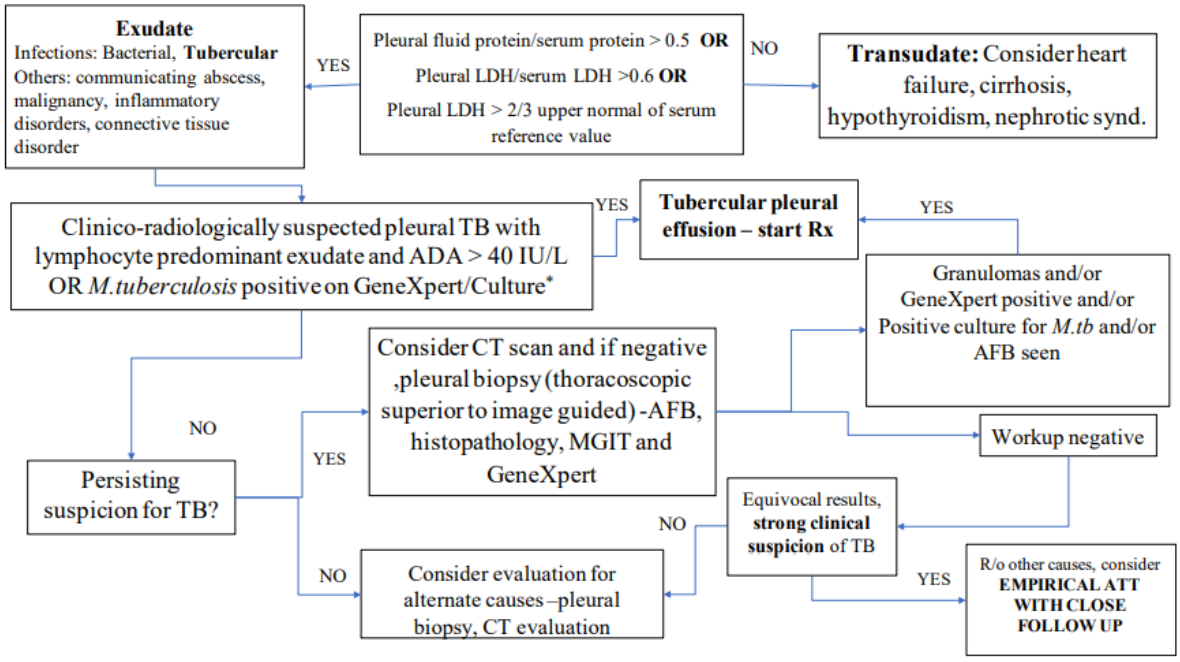
Rule out contraindications to tap –
Platelets <50,000/uL
INR >2
Consider correction if abnormal

Diagnostic pleural tap*



For ALL patients:
Pleural fluid – total counts, differential cell count, glucose, protein, ADA, cytology

For clinically suspected cases:
Bacterial and fungal cultures maybe sent as well



Standards for TB Care in India

Standard 7: Treatment with first-line regimen

7.1 Treatment of New TB patients:

- The initial phase - H, R, Z, E for two months
- The continuation phase - H, R, E for at least four months

7.2 Extension of Continuation Phase: Extend CP by 3 to 6 months in special situations like Bone & Joint TB, Spinal TB with neurological involvement and neuro-tuberculosis.

7.3 Drug Dosages: As per body weight in weight bands

7.4 Bioavailability of Drugs: ensured for every batch

7.5 Dosage frequency:

- Daily/ Intermittent regimen
- OR to assess the feasibility of daily observed therapy under programmatic settings.

7.6 Drug formulations: FDCs may be considered if the recommendations are accepted.

7.7 Previously treated TB patients: No MDR :- 2HREZS/1HREZ/5HRE or 2H3R3E3Z3S3/1H3R3E3Z3/5H3R3E3

4FDC


24 x 28 Tablets
Rifampicin, Isoniazid, Pyrazinamide and Ethambutol Hydrochloride Tablets U.S.P.
Each film coated tablet contains:
Rifampicin U.S.P 150 mg
Isoniazid U.S.P 75 mg
Pyrazinamide U.S.P 400 mg
Ethambutol Hydrochloride U.S.P 275 mg
Approved colours used.
Store below 25°C, protected from excessive humidity.
Protect from light.
Dosage : As directed by the physician.
Keep out of reach of children.
8 901107 016623
Manufactured by :
LUPIN LTD.
A-28/1, M.I.D.C. Chikalthana,
Aurangabad - 431 210. INDIA

3FDC


24 x 28 Tablets
Rifampicin, Isoniazid and Ethambutol Hydrochloride Tablets
Each film coated tablet contains :
Rifampicin U.S.P 150 mg
Isoniazid U.S.P 75 mg
Ethambutol Hydrochloride U.S.P 275 mg
Approved colours used
Store below 25°C, protected from excessive humidity.
Protect from light.
Dosage : As directed by the physician.
Keep out of reach of children.
8 901107 016845
Manufactured by :
LUPIN LTD.
A-28/1, M.I.D.C. Chikalthana,
Aurangabad - 431 210. INDIA

Daily Dose Schedule for Adults
(as per weight bands)

Weight band	Number of tablets	
	Intensive phase	Continuation phase
	HRZE	HRE
	75/150/400/275 mg	75/150/275 mg
25-34kg	2	2
35-49kg	3	3
50-64kg	4	4
65-75 kg	5	5
> 75 kg	6	6

FDCs – Background

Fixed Dose Combinations (FDCs) refer to products containing two or more active ingredients used for a particular indication(s)

FDCs are already in use by National AIDS Control Programme and National Vector Borne Disease Control Programme

STCI/WHO has advocated replacing single-drug regimens for treatment of primary TB with fixed-dose combinations

IMAGING IN PULMONARY TUBERCULOSIS

Dr. Swizzel Pereira

INTRODUCTION

- Tuberculosis is a widespread problem, especially in our countray where it is a leading cause of mortality.
- Though various radiological modalities are widely used in evaluation of patients, no imaging guidelines exist for the use of these modalities in diagnosis and follow up.
- Imaging is not optimally utilized and patients are often unecessarily subjected to repeated CT examinations
- The current guidelines for diagnosis of adult chest tuberculosis (TB) are based primarily on the **demonstration of acid-fast bacilli (AFB) on sputum microscopy.**
- Chest radiograph (CXR) finds its place in **sputum-negative patients** not responding to a course of antibiotics.
- Though computed tomography (CT) is frequently employed in the diagnosis and follow-up of TB, it **does not find a place in the national and international guidelines.**
- With India having a large burden of TB, it is important to have established imaging criteria and recommendations.

IMAGING MODALITIES

CHEST X-RAY

- Sputum smear microscopy, culture for AFB, and CXR postero-anterior (PA) view are the initial investigations performed in adults suspected to have TB.
- CXR is frequently employed as the initial test to evaluate unexplained cough.
- It is the primary modality for diagnosis and follow-up, and may be the only imaging required in sputum-positive cases.
- Apicogram/lordotic view (for lung apices) and lateral view are of limited utility and CT is the next investigation in case of equivocal CXR.
- CXR is useful to look for any evidence of PTB as well as to identify other abnormalities responsible for the symptoms.

CHEST CT

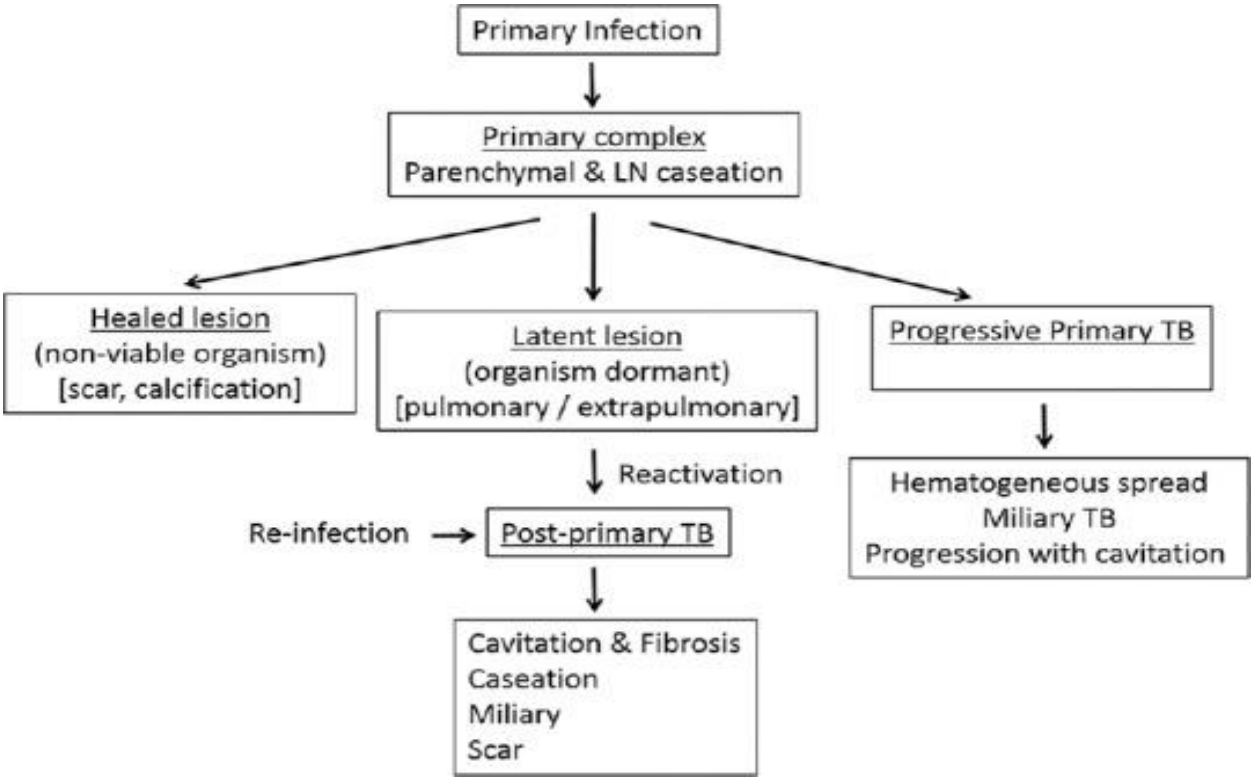
- Important tool in the detection of radiographically occult disease, differential diagnosis of parenchymal lesions, evaluation of mediastinal lymph nodes, assessing disease activity, and evaluating complications.

- Enables earlier and more accurate diagnosis of pulmonary lesions
- Enables evaluation of bronchiectasis, cavitation, associated fungal balls, and assessment of necrosis in the LNs, identifying pleural/airway/diaphragmatic pathologies and evaluating visualized bones.
- CECT is the investigation of choice for evaluation of mediastinal LNs and also aids in depicting pleural enhancement in empyema.
- High-resolution CT (HRCT) reconstructions useful to detect miliary and centrilobular nodules, ground-glass opacities, and air-trapping.
- The value of CT lies in the fact that it enables one to suggest a diagnosis of TB in patients with negative sputum examination and those without sputum production. Moreover, CT findings may permit empirical initiation of ATT until the time culture results are obtained.

When to do chest radiograph?	When to do CT?
Evaluation of patients suspected to have TB	Evaluation of patients suspected to have TB
Evaluation of patients with unexplained cough and expectoration	For diagnosis of CTB in case of sputum negative patient with equivocal CXR or/and equivocal clinical profile)
Evaluation of unexplained fever or constitutional symptoms (loss of appetite or weight)	Initial CECT for complete disease assessment in patients suspected to have additional extrathoracic involvement
In a patient suspected/diagnosed to have extrathoracic TB, as a baseline work-up	In a diagnosed case of CTB for assessment of disease activity in case of
In a diagnosed case of CTB	Persistent lesions (pulmonary/nodal/effusion) on CXR
After the completion of intensive phase, for assessing treatment response	Radiographic worsening
After the completion of treatment regimen in selected cases (refer flowcharts)	Equivocal CXR in absence of clinical response
After any intervention (chest tube, etc.)	In evaluation of symptomatic patients with suspected TB sequelae: when no prior radiographs available for comparison or if evolution of new findings
In evaluation of symptomatic patients (e.g hemoptysis, dyspnea, cough with expectoration) with past history of TB	Imaging of suspected complications of TB

CT: Computed tomography, CTB: Chest tuberculosis, TB: Tuberculosis, CXR: Chest radiograph

PRIMARY V/S POST PRIMARY TUBERCULOSIS



PRIMARY TUBERCULOSIS

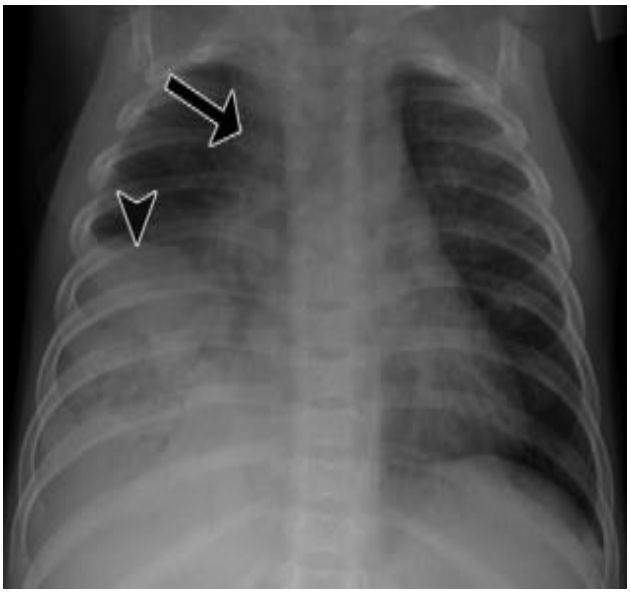
LYMPHADENOPATHY

- Most common radiologic manifestation of primary tuberculosis.
- Seen in 83%–96% of pediatric cases (may be the only radiologic finding) and 10%–43% of adult cases
- Typically involves the **right paratracheal and hilar lymph nodes**
- Typically demonstrates a **low-attenuation center with peripheral rim enhancement on CECT images** (due to central caseous necrosis with peripheral granulomatous inflammatory tissue).

At resolution of lymphadenopathy, calcified normal-sized lymph nodes may rema

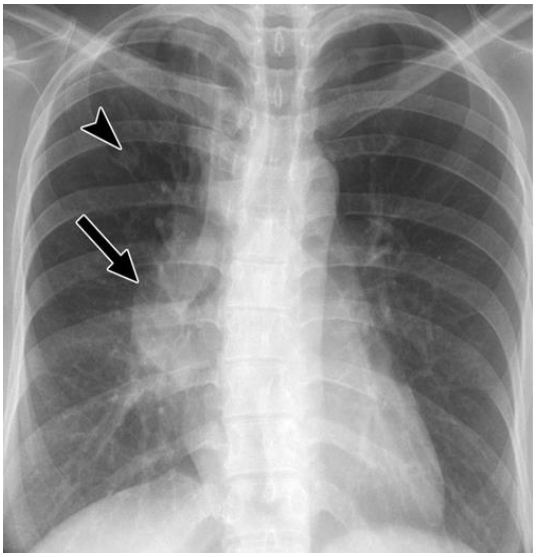
Lymphadenopathy and consolidation in a 6-month-old infant with primary tuberculosis

Thickening of the right paratracheal stripe consistent with lymphadenopathy (arrow), and consolidation (arrowhead) in the right middle and lower lobe

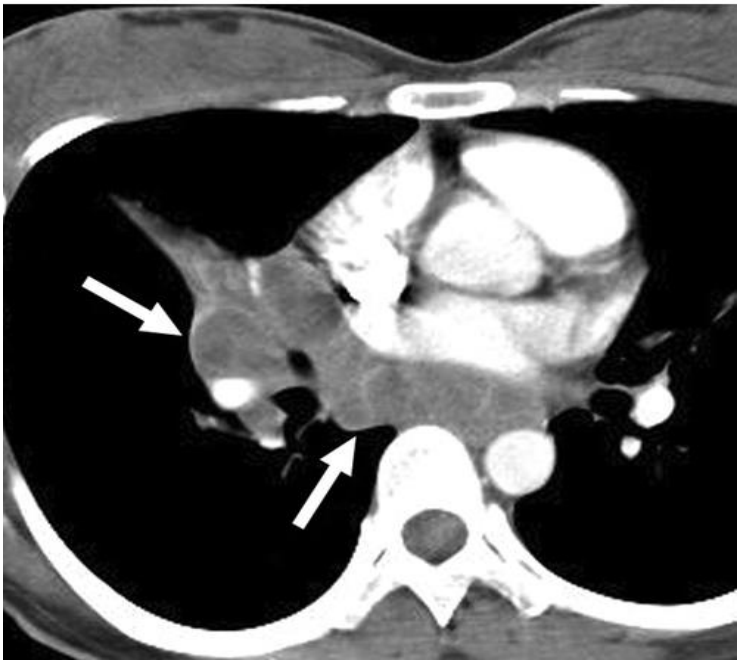


Primary tuberculosis manifesting primarily as lymphadenopathy

Posteroanterior chest radiograph shows right hilar mass (arrow). Note smaller nodule (arrowhead) in right upper lung zone.



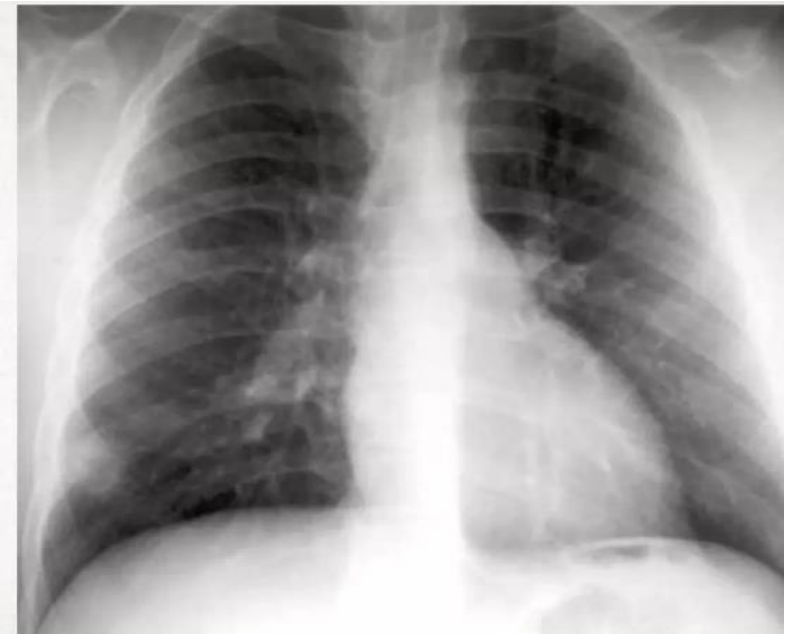
CECT scan shows enlarged right hilar and subcarinal lymph nodes (arrows), central necrotic low attenuation, and peripheral rim enhancement.



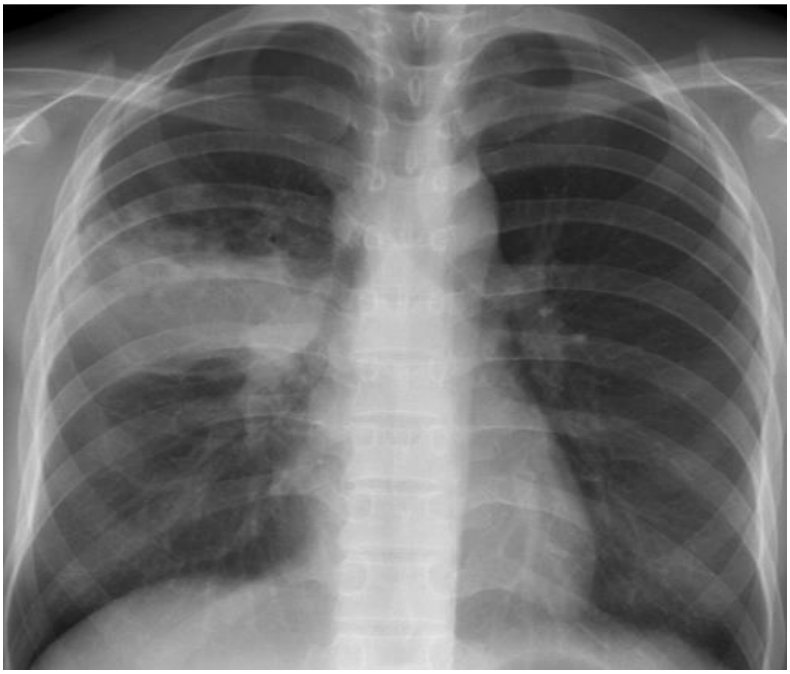
PARENCHYMAL DISEASE

- **Most frequently manifests as consolidation**
- Depicted as an area of opacity in a segmental or lobar distribution.
- There is no strong lobar predilection in primary tuberculosis
- Cavitation occurs in a minority of patients
- When cavitation occurs, it is known as progressive primary disease. This cavitation occurs within existing consolidation and thus does not demonstrate an upper lung zone predominance, in contrast to postprimary disease.

GHONS COMPLEX

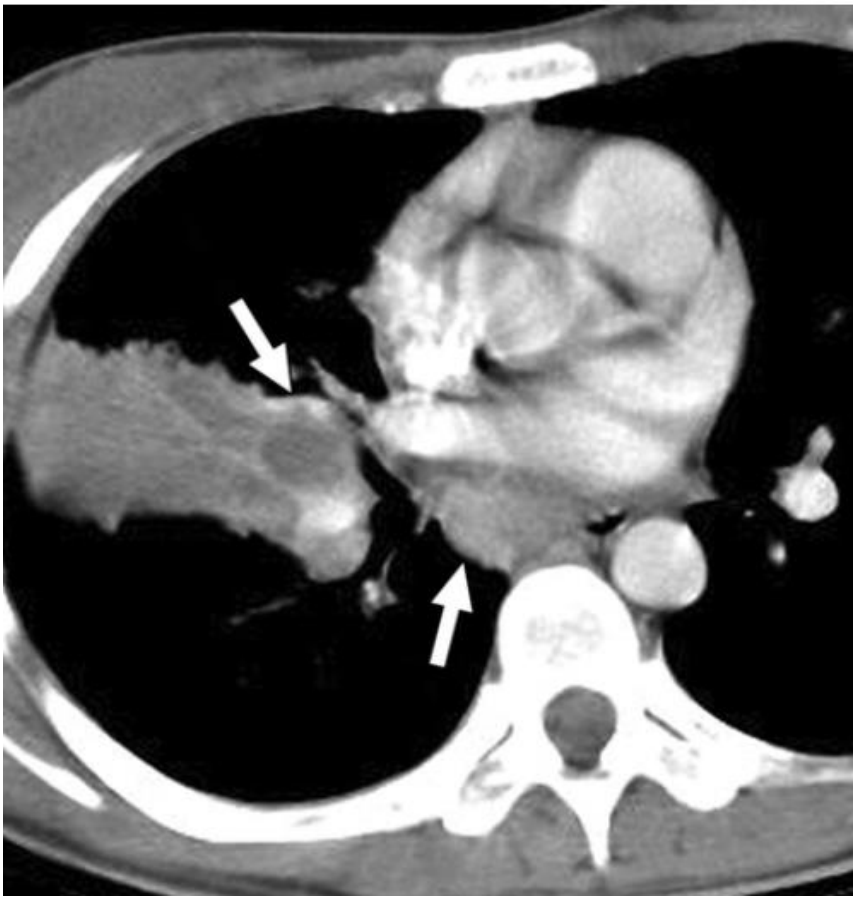


Posteroanterior chest radiograph shows airspace consolidation in right middle lung zone.



CECT shows airspace consolidation in right middle lobe.

Note enlarged right hilar and subcarinal lymph nodes (arrows). Hilar node has necrotic low attenuation.

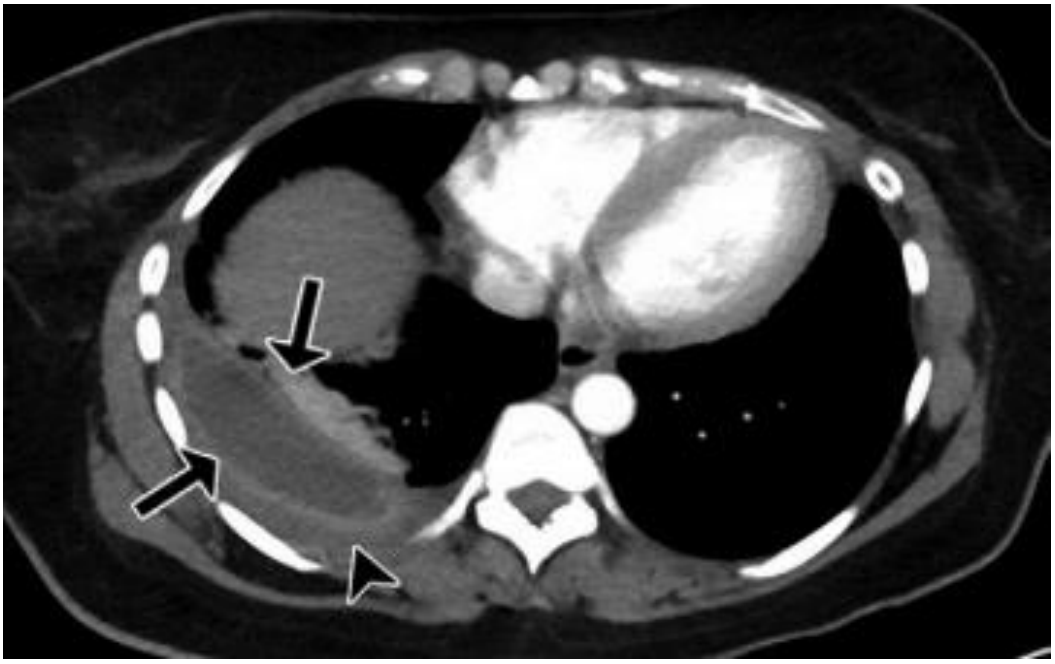


PLEURAL EFFUSION

- Seen in ~25% of primary tuberculosis cases in adults, with the vast majority of such effusions being unilateral.
- Less common in children
- Less common in postprimary disease.
- Result from hypersensitivity to tuberculous protein, rather than frank pleural
- infection
- Tuberculous empyemas are typically **loculated** and associated with **pleural thickening and enhancement**.
- If not treated early, may be complicated with **broncho-pleural fistula** or extension into the chest wall (**empyema necessitatis**).
- An air-fluid level within an empyema in the absence of instrumentation is suggestive of a bronchopleural fistula.
- After treatment and healing, residual pleural thickening with calcification can develop, potentially leading to fibrothorax.

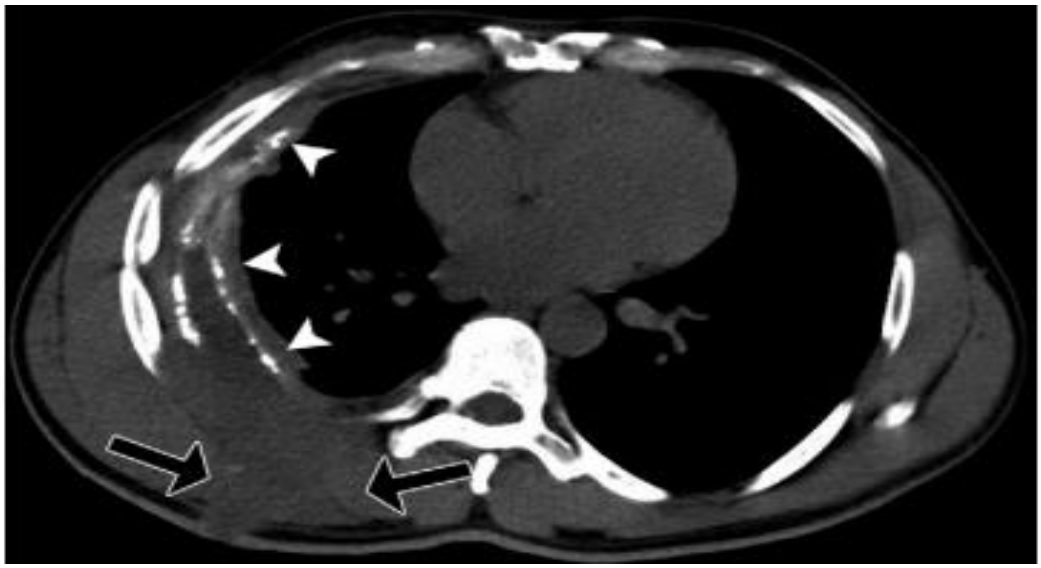
Tuberculous empyema in a 40-year-old woman

CECT image shows a loculated right-sided pleural effusion with thickened, enhancing pleura (arrows) as well as infiltration of the extrapleural fat (arrowhead)



Empyema necessitaNS

Axial nonenhanced chest CT image shows pleural calcifications (arrowheads), a loculated pleural effusion with marked pleural thickening, and extension into the chest wall (arrows).



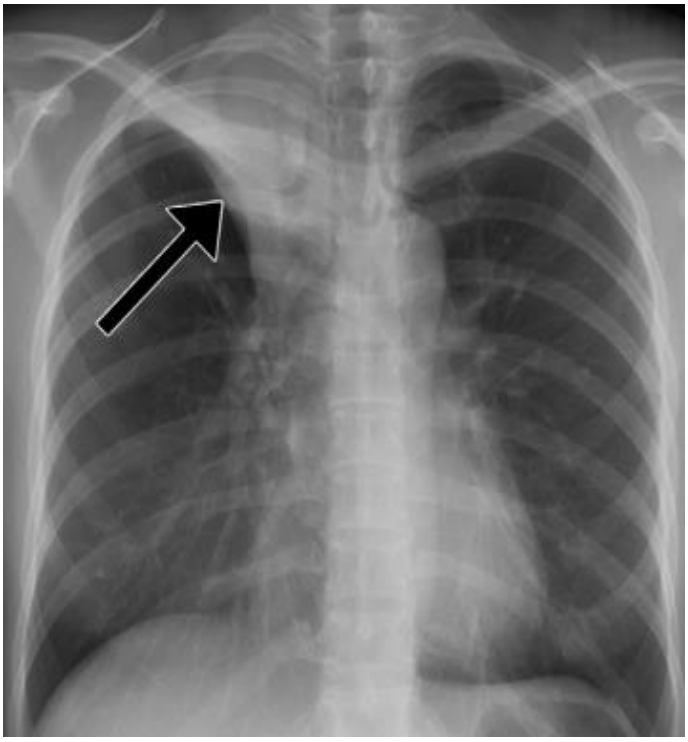
AIRWAY DISEASE

- Bronchial wall involvement may be seen in primary and postprimary tuberculosis, although it is more common in the former

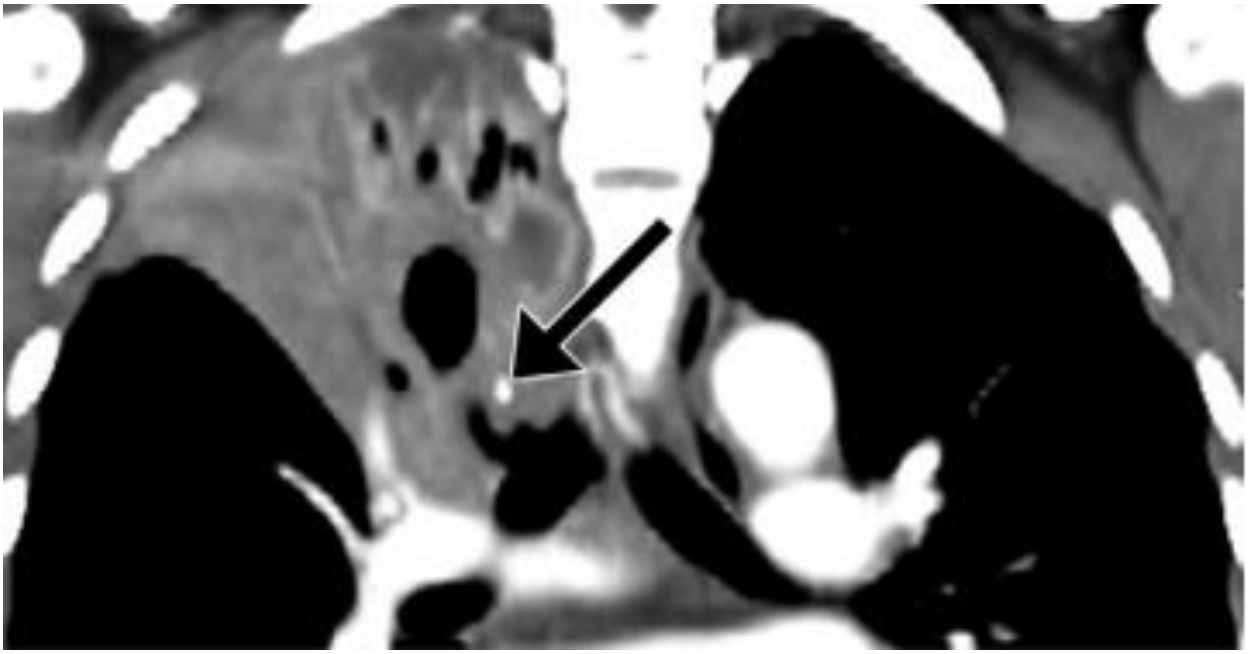
- Occurs due to direct extension from tuberculosis lymphadenitis by means of endobronchial or lymphatic dissemination.
- The main radiographic features of proximal airway involvement are indirect, including **segmental or lobar atelectasis**, **lobar hyperinflation, mucoid impaction, and post obstructive pneumonia.**
- At CT, airway involvement can manifest as **long segment narrowing with irregular wall thickening, luminal obstruction, and extrinsic compression.**

Airway involvement with tuberculosis

PA chest radiograph shows right upper lobe collapse (arrow).



Coronal reformatted CECT image at the level of the central bronchi shows irregular thickening of the right upper lobe bronchus (arrow), as well as right upper lobe volume loss



POST PRIMARY TUBERCULOSIS

PPT is characterized by:

1. Liquefaction of caseous necrosis,

2. Formation of cavities,

3. Progressive fibrosis and lung destruction,

4. Bronchogenic spread.

- The **apical and upper lung zone predominance** may be related to the relatively reduced lymphatic drainage and increased oxygen tension in these regions, factors that facilitate bacillary replication.
- A chest radiograph is typically obtained to evaluate for findings of active disease.
- Chest CT may be useful in identifying active tuberculosis even if the chest radiograph is negative although chest CT is not the standard of practice

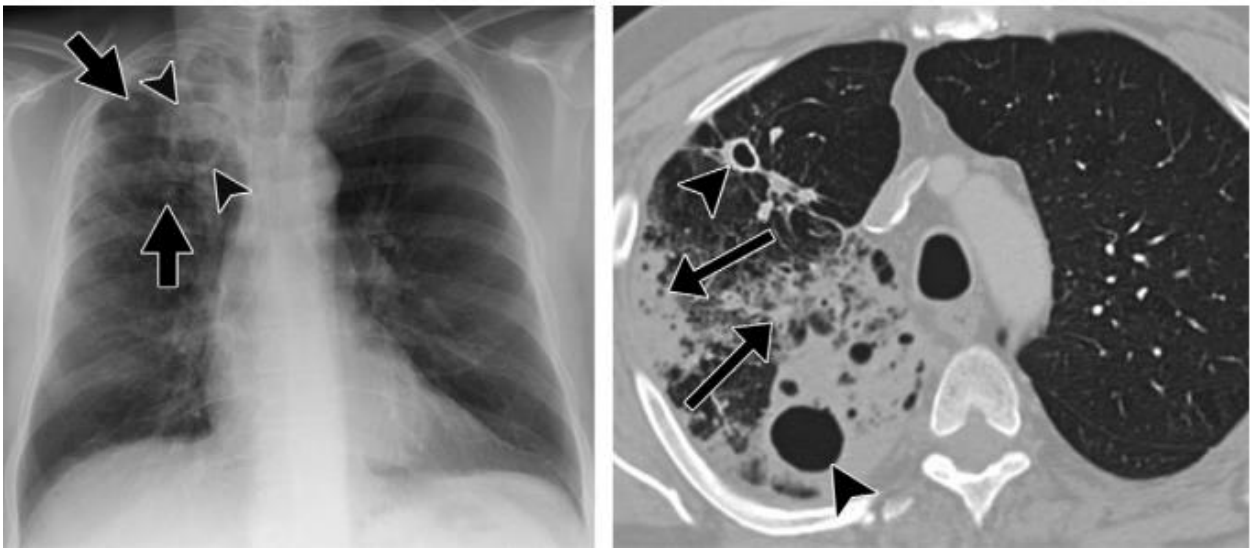
CONSOLIDATION AND CAVITATION

- **Patchy, poorly marginated consolidation** is an early and consistent feature of postprimary tuberculosis.

In 3%–6% of cases of postprimary tuberculosis, a noncalcified nodule known as a **tuberculoma** (ranging from 5 mm to 40 mm in largest dimension) may be the predominant manifestation; these tuberculomas are typically solitary and may occur with small satellite nodules

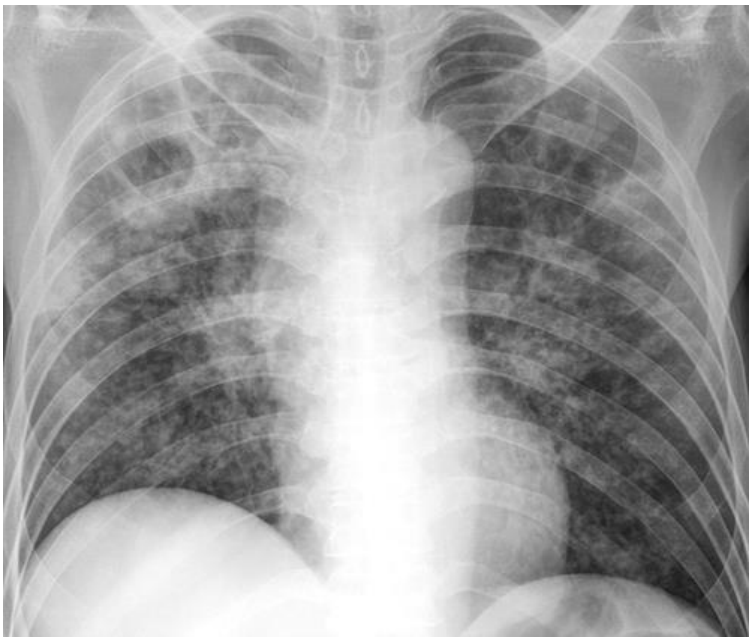
- In postprimary tuberculosis, **cavitation** is a common finding, seen in 20%–45% of patients on chest radiographs.

- Cavities can be several centimeters in largest dimension and can develop thick and irregular walls. Cavitary lesions are often seen within areas of consolidation and may be multifocal.
- Residual cavities may persist after treatment, findings that predispose to bacterial super infection, mycetoma formation, or erosion of adjacent vasculature resulting in hemoptysis.
- The presence of an air-fluid level within a cavity may be related to the tuberculosis itself or to bacterial super infection.

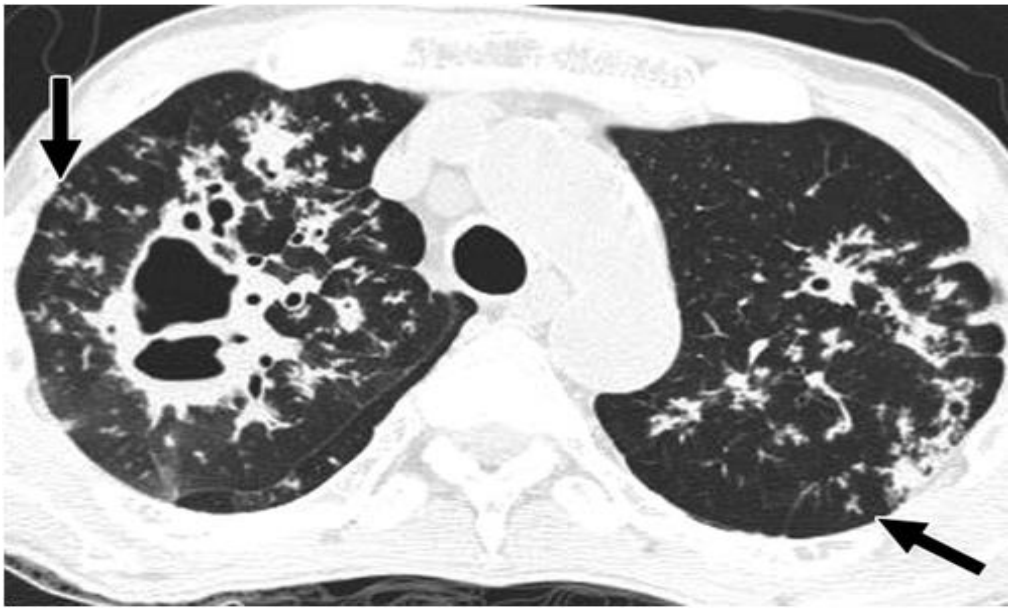


PA chest radiograph shows patchy airspace opacities (arrows) in the right upper lobe, with a cavitary lesion (arrowheads).

Axial chest CT image shows right upper lobe consolidation (arrows) with associated cavitation (arrowheads).

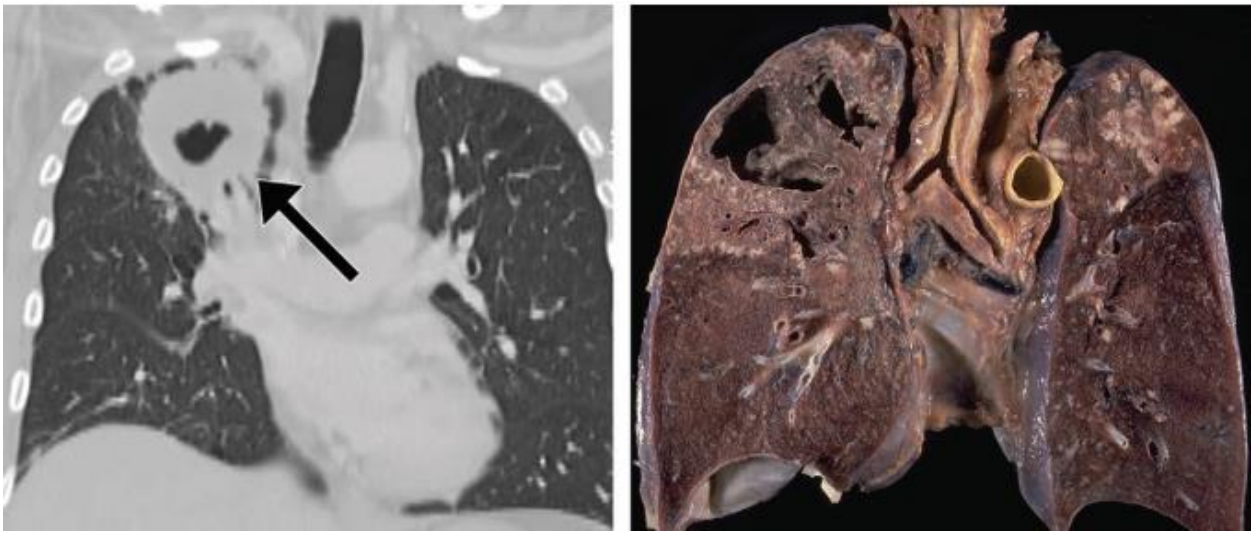


AP CXR shows cavitary consolidation in right upper zone and multiple ill-defined nodules in both lungs.

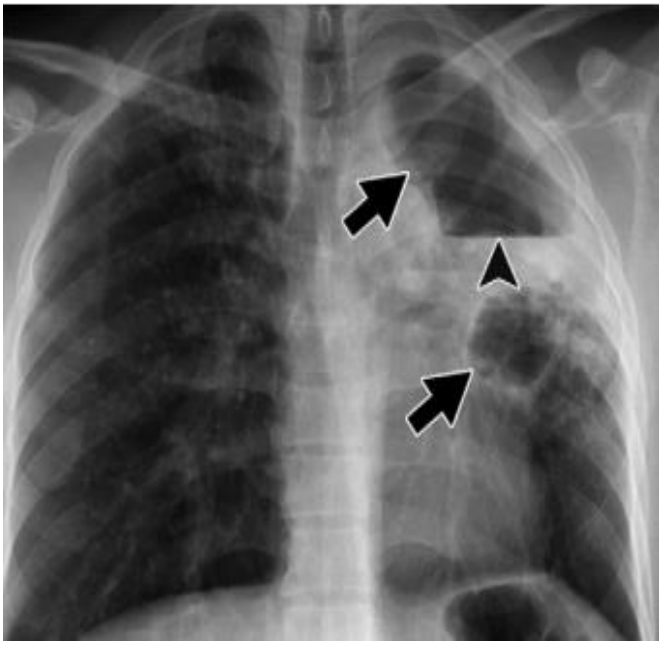


HRCT scan shows consolidation and acinus-sized nodules containing several cavities in both upper lobes.

Note branching nodular and linear opacities (tree-in-bud signs) (arrows) and centrilobular small nodules in both lungs.



Coronal chest CT image shows a thick-walled cavitary lesion (arrow) in the right upper lobe. Photograph of a gross lung specimen shows necrotizing consolidation in the right upper lobe, which has developed several cavities. Consolidation is also noted in the left upper lobe.



PA CXR shows two left-sided cavitary lesions (arrows), with an air-fluid level in the larger lesion (arrowhead), and scattered reticulonodular opacities.

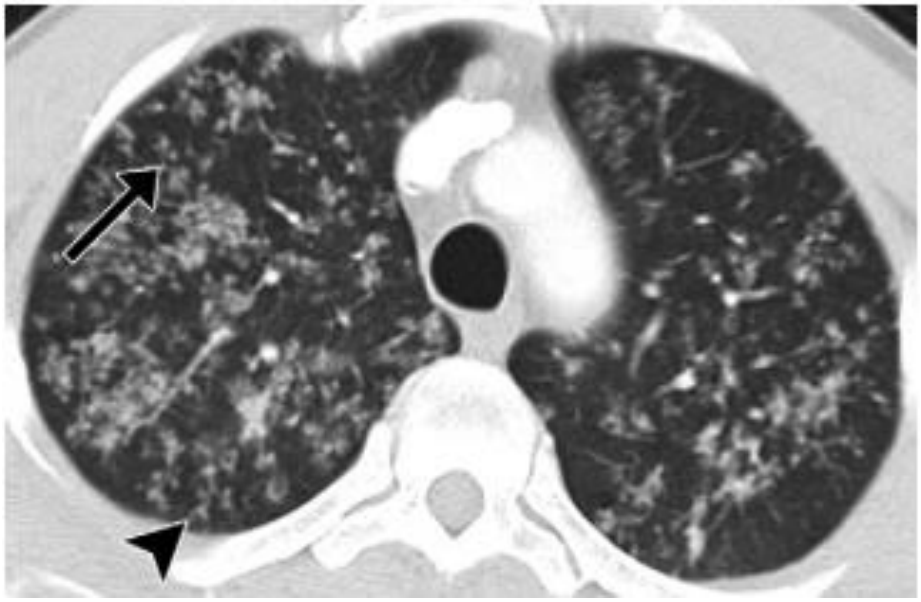
CENTRILOBULAR NODULES

- Active tuberculosis often communicates with the bronchial tree, which results in endobronchial spread.
- Histologically, caseous necrosis and granulomatous inflammation fill respiratory bronchioles and alveolar ducts

- This histologic finding manifests radiologically as **centrilobular nodules and the tree-in-bud sign.**
- Centrilobular nodules are seen in approximately 95% of cases of active tuberculosis.
- Unlike cavitary lesions and consolidation, centrilobular nodules may be seen in the lower lobes, distant from the cavitary lesions.
- Involvement of the airways and pleura is less common in post primary than in primary tuberculosis but shows similar imaging features.

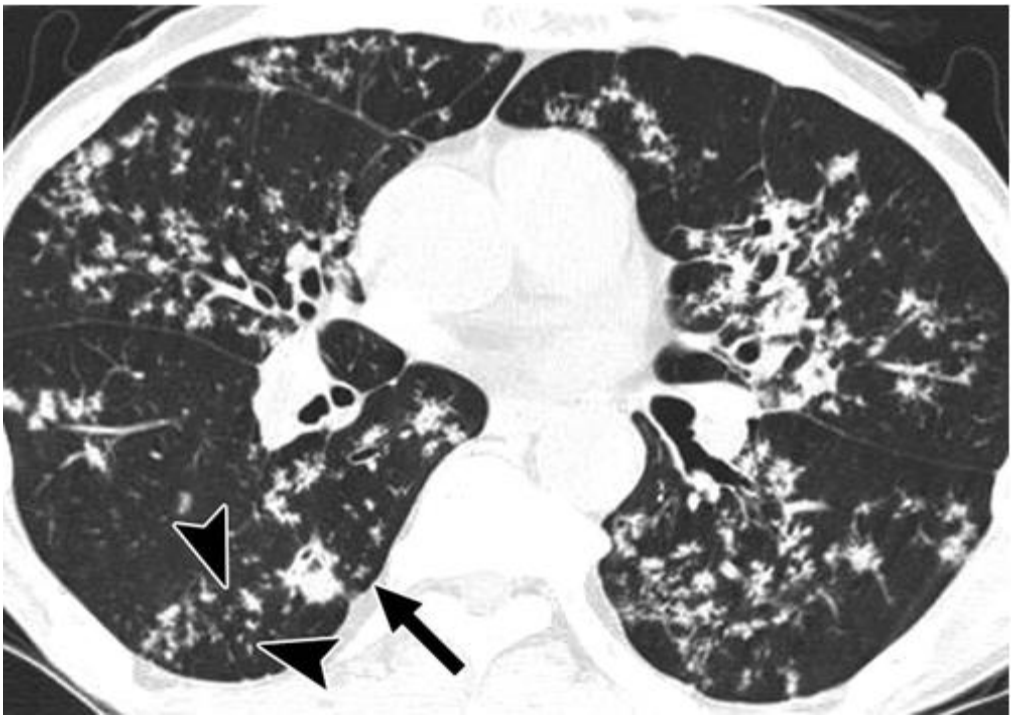
Airway dissemination of tuberculosis

Axial chest CT image shows centrilobular (arrow) and tree-in-bud (arrowhead) nodules, as well as more confluent areas of consolidation



HRCT scan shows consolidation and acinus-sized nodules containing several cavities in both upper lobes.

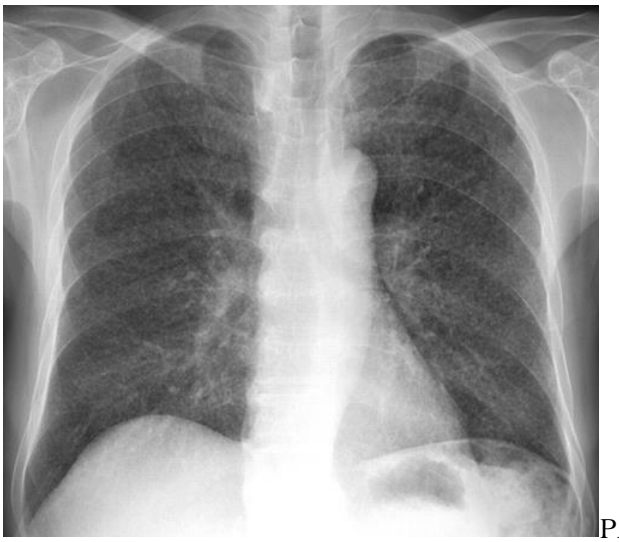
Note branching nodular and linear opacities (tree-in-bud signs) (arrows) and centrilobular small nodules (arrowheads) in both lungs.

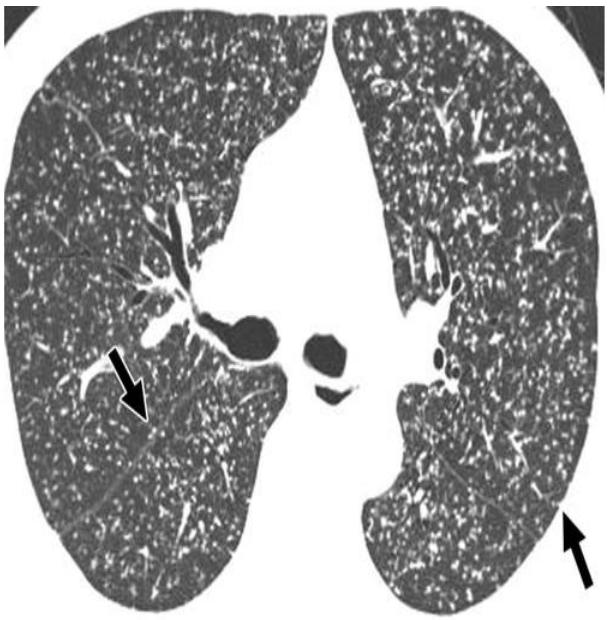


TUBERCULOSIS IN AN IMMUNOCOMPROMISED HOST

- Immunocompromised patients are at a higher risk of developing primary and postprimary tuberculosis.
- Although most tuberculosis cases in immunocompromised individuals are related to reactivation of latent tuberculosis, the radiologic and clinical manifestation more closely resemble those of primary tuberculosis (ie, with consolidation and lymphadenopathy)
- In severely immunosuppressed patients with pulmonary tuberculosis, chest radiographs may be normal 10%–40% of the time.
- Miliary tuberculosis also occurs at a higher rate in patients with severe immunosuppression.

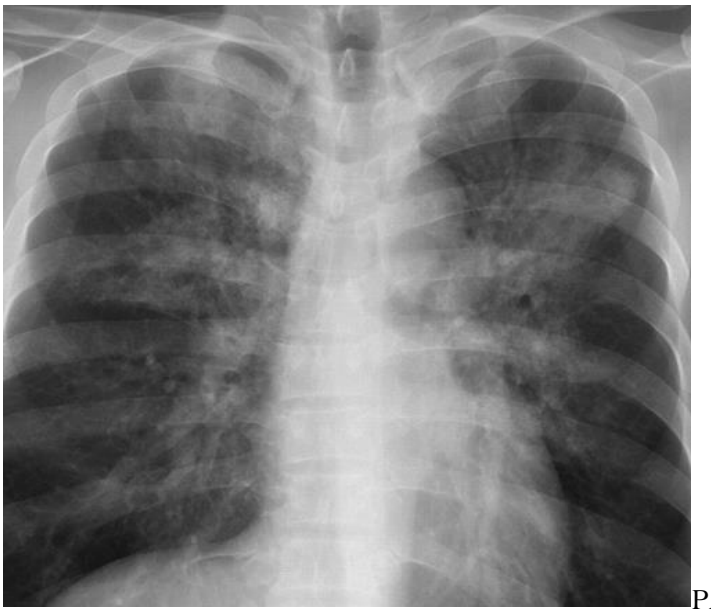
MILIARY TUBERCULOSIS

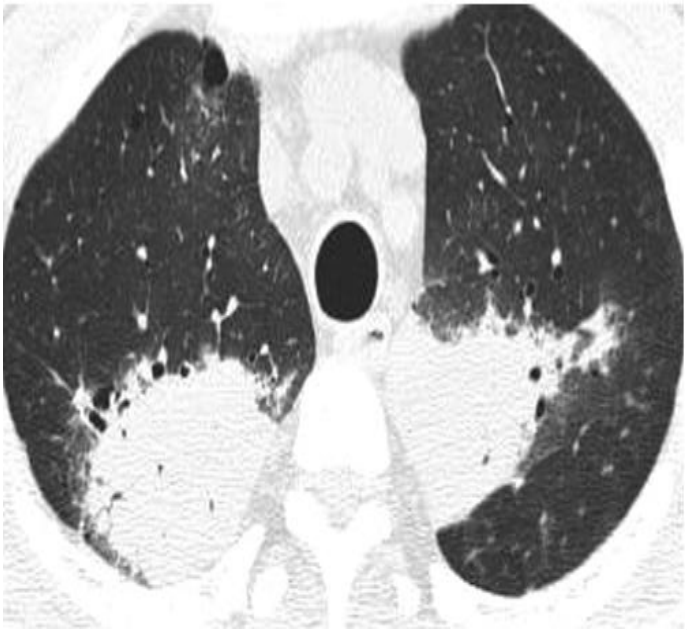

PA CXR shows evenly distributed, discrete, uniformly sized, millet-sized nodular opacities in both lungs.


HRCT shows uniform-sized small nodules randomly distributed throughout both lungs

- The radiographic manifestations of HIV-associated pulmonary TB are thought to be dependent on the level of immunosuppression at the time of overt disease.
- On CT, HIV-seropositive patients with a CD4 T lymphocyte count <200/mm3 have a higher prevalence of mediastinal or hilar lymphadenopathy, a lower prevalence of cavitation, and often extrapulmonary involvement as compared with HIV-seropositive patients with a CD4 T lymphocyte count equal to or ≥ 200/mm3

Pulmonary tuberculosis in 51-year-old man with AIDS. (CD4 count=4 cells/µL)


PA CXR shows multifocal mass like airspace consolidation in bilateral upper lung zones.


Mass like airspace consolidation with air bronchograms, centrilobular small nodules and ground-glass opacity in both upper lobes.

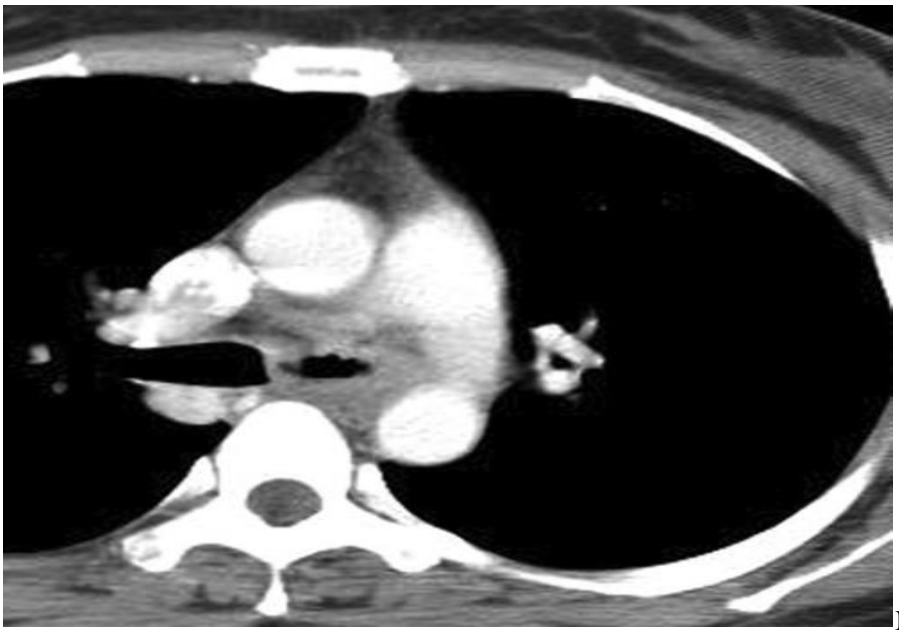
TRACHEOBRONCHIAL TUBERCULOSIS

- It usually occurs as a complication of primary TB, originating from perforation of an involved LN into a bronchus, though it may occur in PPT as well by ascending endobronchial spread.

- CT in **acute tracheobronchitis** may reveal **circumferential narrowing** of the involved segment associated with smooth or irregular wall thickening with abnormal enhancement and adjacent adenopathy.
- This granulomatous involvement of the tracheobronchial tree can ulcerate, which on healing produces **fibrotic bronchostenosis and post-obstructive bronchiectasis**.

Long segment involvement is common and left main bronchus is most frequently involved.

- These bronchial strictures can lead to **lobar or segmental collapse**


Luminal narrowing of trachea and proximal left main bronchus and irregular wall thickening.

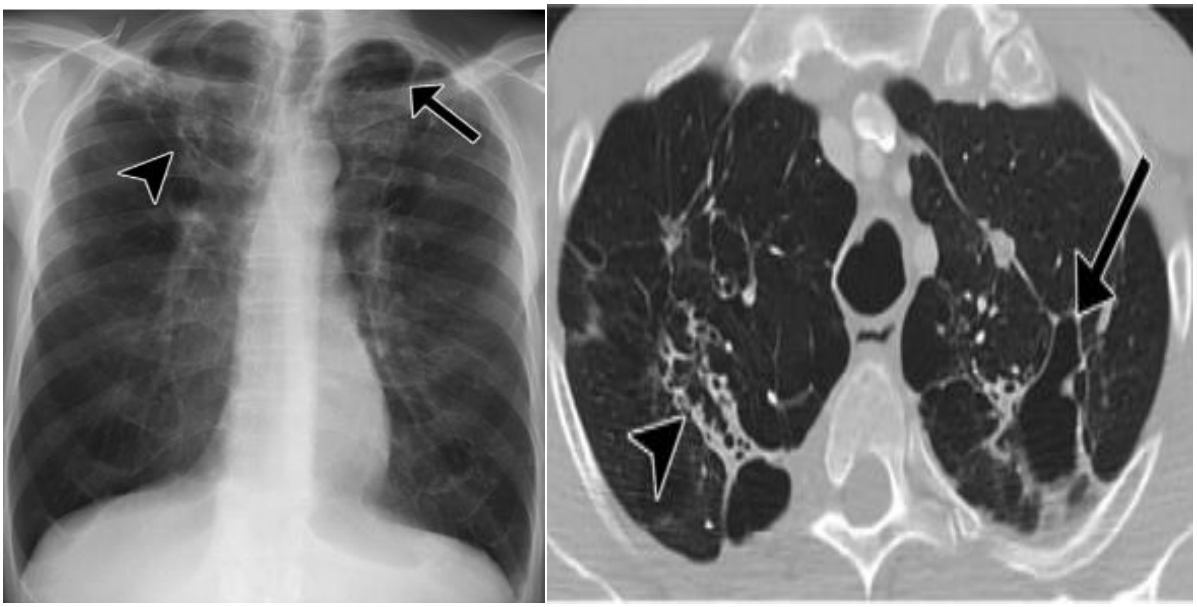
INACTIVE TUBERCULOSIS

- By definition, previous (inactive) disease demonstrates **radiographic or clinical evidence of previous tuberculosis but no evidence of currently active tuberculosis**
- Characterized by **stable** fibronodular changes, including scarring (peri_x0002_bronchial fibrosis, bronchiectasis, and architec_x0002_tural distortion) and nodular opacities in the api_x0002_cal and upper lung zones.
- Fibronodular change - associated with higher risk of developing tuberculosis reactivation.
- Calcified granulomas and calcified lymph nodes - associated with extremely low risk of reactivation.

Healed tuberculosis cavities may persist after active disease resolves and can be complicated by hemoptysis, bacterial infection, or mycetoma

- CXR are important in the evaluation and risk stratification of patients suspected of having latent or inactive tuberculosis.
- Radiology reports should describe whether the radiograph shows entirely normal findings, shows calcified granulomas, shows fibro nodular scarring, or shows findings that raise concern for active tuberculosis.

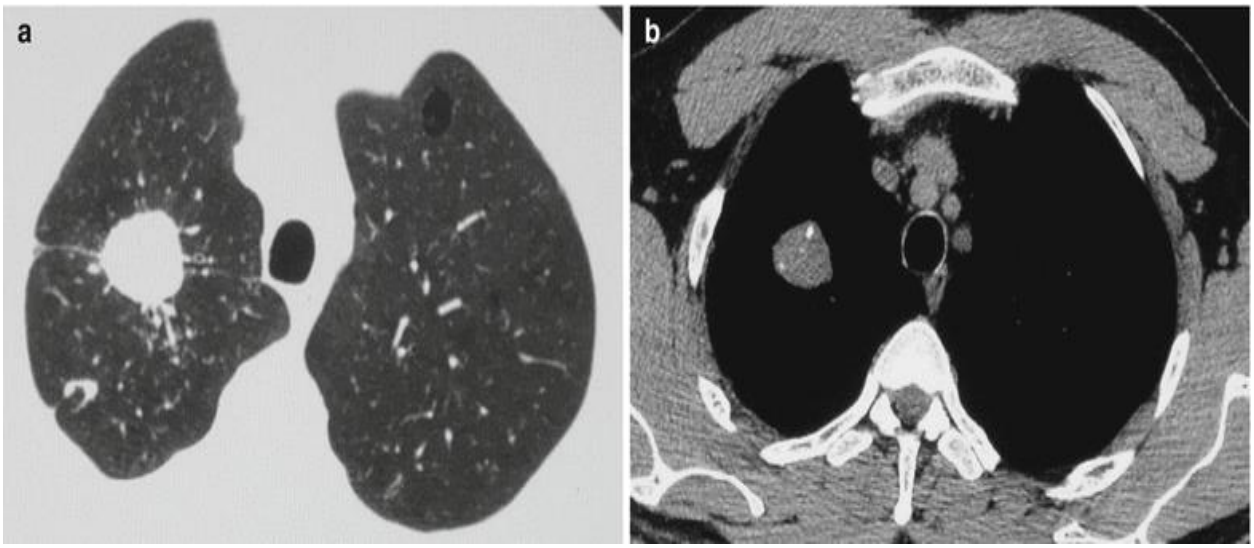
It is important to remember that any finding that raises the possibility of active tuberculosis should prompt communication with the referring provider and placement of the patient in respiratory isolation



PA chest radiograph shows upper lobe fibrosis (arrowhead) and volume loss with a residual cavity (arrow).

Axial CT image shows peribronchial fibrosis (arrowhead) and architectural distortion in the lung apices, with a residual cavity (arrow).

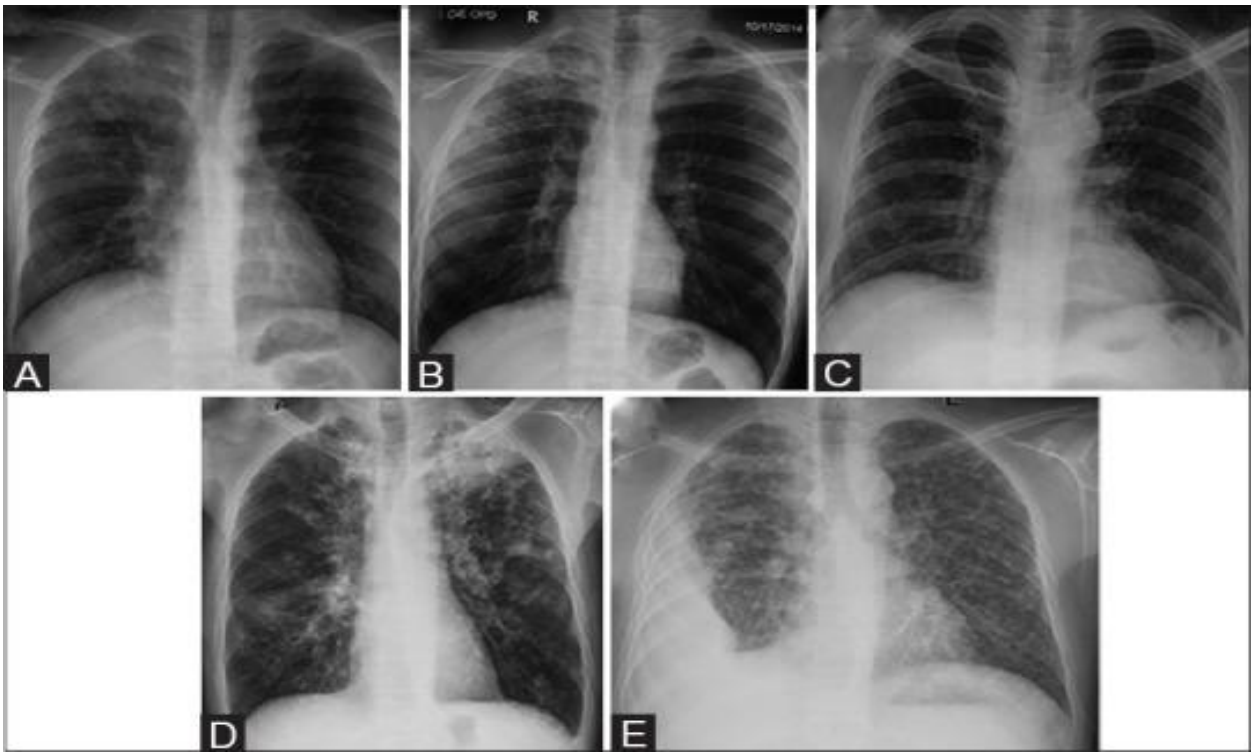
TUBERCULOMA- SIGN OF INACTIVE TB



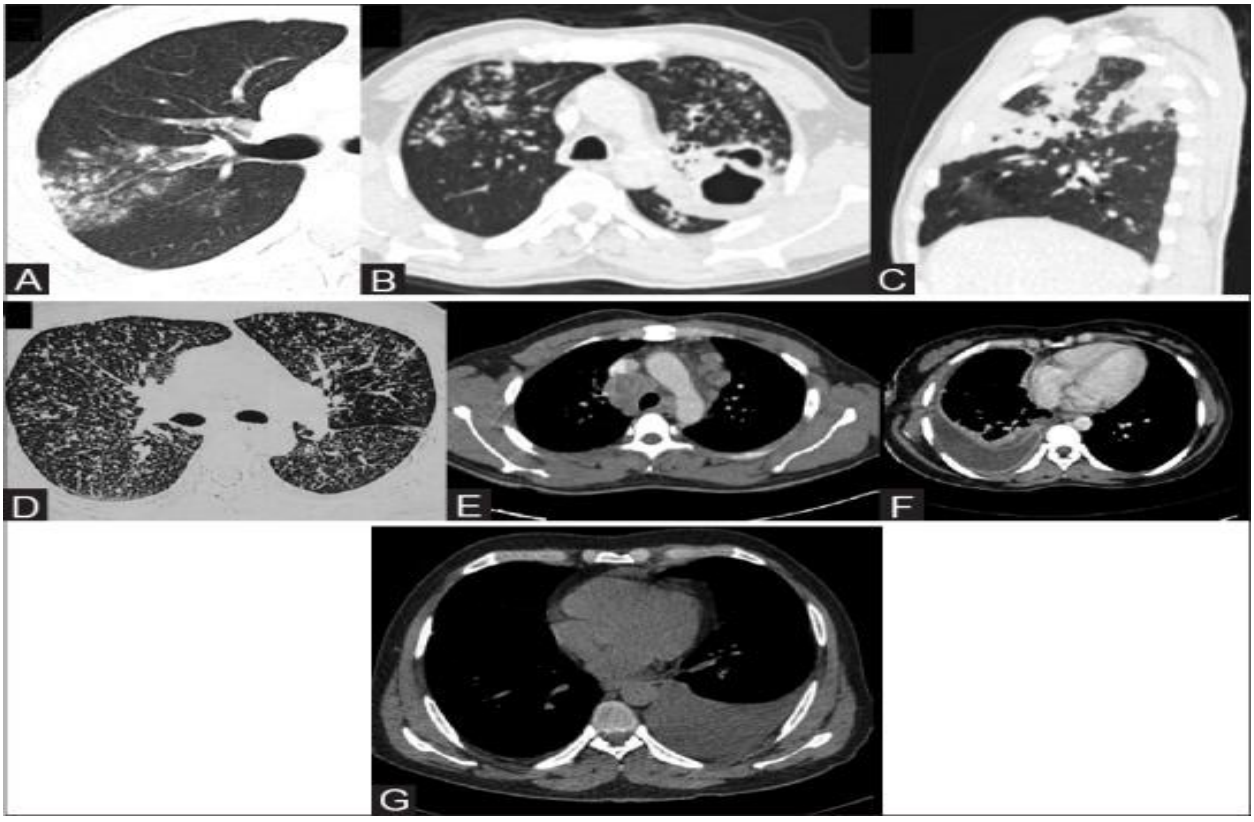
Definitive of active TB	Indeterminate for disease activity	Healed TB
CXR	CXR	CXR
Air-space nodules/clustered nodules in upper/midzones	Consolidation/air-space nodules/clustered nodules in lower zones	Thin-walled cavity ± aspergilloma
Consolidation in upper/midzones with ipsilateral LN enlargement	Equivocal nodules (miliary/air space)	Bronchiectasis
Miliary nodules	Cavity with air-fluid level	Fibroparenchymal/reticular opacities
Thick-walled cavity	Equivocal hilar prominence/widening of paratracheal stripe	Atelectasis/collapse
Cavity with surrounding consolidation		Calcified mediastinal LNs
Unilateral hilar/paratracheal LN enlargement		Pleural thickening/calcification
Effusion/empyema		
CT	CT	CT
Air-space nodules/centrilobular nodules/clustered nodules in apical and posterior segments RUL, apicoposterior segment LUL, RML, lingula, superior segment any LL	Consolidation/centrilobular nodules in other segments	Thin-walled cavity
Consolidation in above mentioned regions with ipsilateral LN enlargement	Ground glass opacities: may suggest superimposed secondary infections or aspiration related	Bronchiectasis ± bronchial wall thickening
Miliary nodules	Cavity with air-fluid level: usually indicates secondary infection	Fibroparenchymal opacities
Thick-walled cavity		Atelectasis/collapse
Cavity with surrounding consolidation	Borderline enlarged discrete LNs with homogeneous enhancement or preserved perinodal fat	Well defined small nodules ± calcification
Enlarged mediastinal LNs with central necrosis (rim enhancement) or heterogeneous enhancement		Subcentimetric LNs ± calcification
Conglomeration of LNs or obscuration of perinodal fat		Pleural thickening/calcification
Effusion/empyema with split pleura sign		

CT: Computed tomography, CTB: Chest tuberculosis, TB: Tuberculosis, CXR: Chest radiograph, LNs: Lymph nodes, LUL: Left upper lobe, RML: Right middle lobe

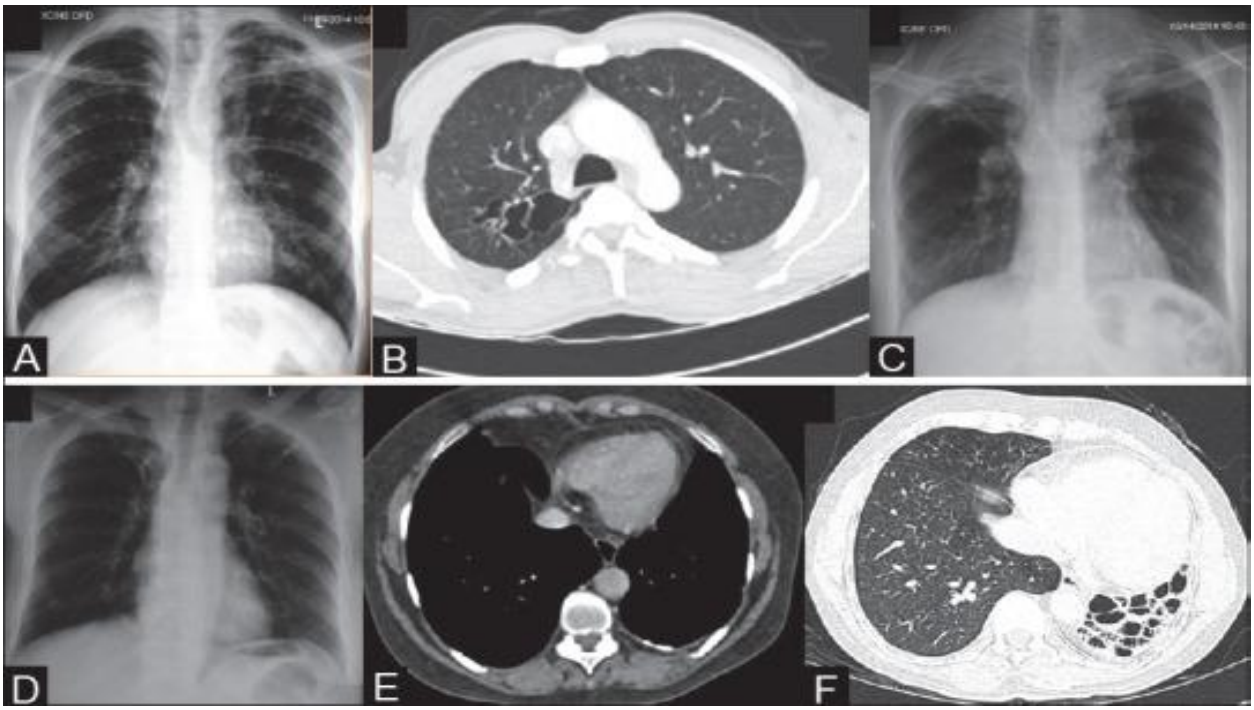
CXR IN ACTIVE TB



CT FINDINGS IN ACTIVE TB



CHEST FINDINGS IN INACTIVE TB



CONCLUSION

- Imaging plays an important role in risk stratification by helping to distinguish latent
- Infection, previous inactive disease, and active disease.
- Imaging findings, such as the presence of cavitation, affect treatment decisions, such as
- The length of a course of therapy for active diseasese.
- The radiologist should be familiar with the imaging findings of pulmonary tuberculosis, as well as the clinical features, risk factors, laboratory tests, and treatment algorithms to contribute more effectively to patient care.

LABORATORY DIAGNOSIS OF TB

Dr. Cigy C.Borges

Causative Agents of TB

- TB is caused by the bacterial species *Mycobacterium tuberculosis* and occasionally by other species belonging to the TB complex (*M. bovis, M. africanum, M. microti)*
- Members of the TB complex are also known as Tubercle Bacilli
- **WORLD TB DAY-24TH MARCH**
- This annual event commemorates the date in 1882 when Dr. Robert Koch announced his discovery of ***Mycobacterium tuberculosis***, the bacillus that causes tuberculosis (TB)
- **TB Diagnostic Laboratory Methods**
- WHO Policies on TB Diagnostics since 2007

TB Diagnostic Laboratory Methods: Microscopy

Ziehl Neelsen(ZN) STAINING

- 10,000 AFB /ml required

- Sensitivity = 50% in pulmonary TB

(much lesser in EP samples)

TB Diagnostic Laboratory Methods: Microscopy

- **Fluorescent microscopy (LED-FM)**: staining with florescent dyes

- > Sensitive than ZN (10%)

- Similar specificity, can read at lower magnification

- Quicker, **1000 AFB/ml required**

Advantages and Limitations of AFB Smear Microscopy

AFB Smear Microscopy

Advantages

Can be done at point-of-care sites by trained technician

Easy to perform and cheap

Monitors treatment success smear positive to smear negative

Limitations

Low sensitivity

Stain both live and dead mycobacteria

Does not differentiate tubercle bacilli from other mycobacteria

Drug susceptibility unknown

TB Diagnostic Laboratory Methods: Culture

GOLD STANDARD (LOD:10-100 bacilli/ml)

Solid culture (LJ): 4-8 weeks

Liquid culture (MGIT 960 system)

Liquid culture is more sensitive and faster than solid culture, but it is expensive

Liquid culture positivity occurs as early as 4-21 days (7-14 days)

TB Diagnostic Laboratory Methods: LC-DST

Phenotypic (Culture-Based) Drug-Susceptibility Testing (DST)

Requires a high level of biosafety precautions

LC DST can be ready at the earliest in 21-28 days by liquid culture

Advantages and Limitations of TB Diagnostic Methods

TB Culture

Advantages

Gold standard, detects small numbers of organisms

Species identification

Follow up monitoring and DST

Drug resistance surveys and Epidemiological studies

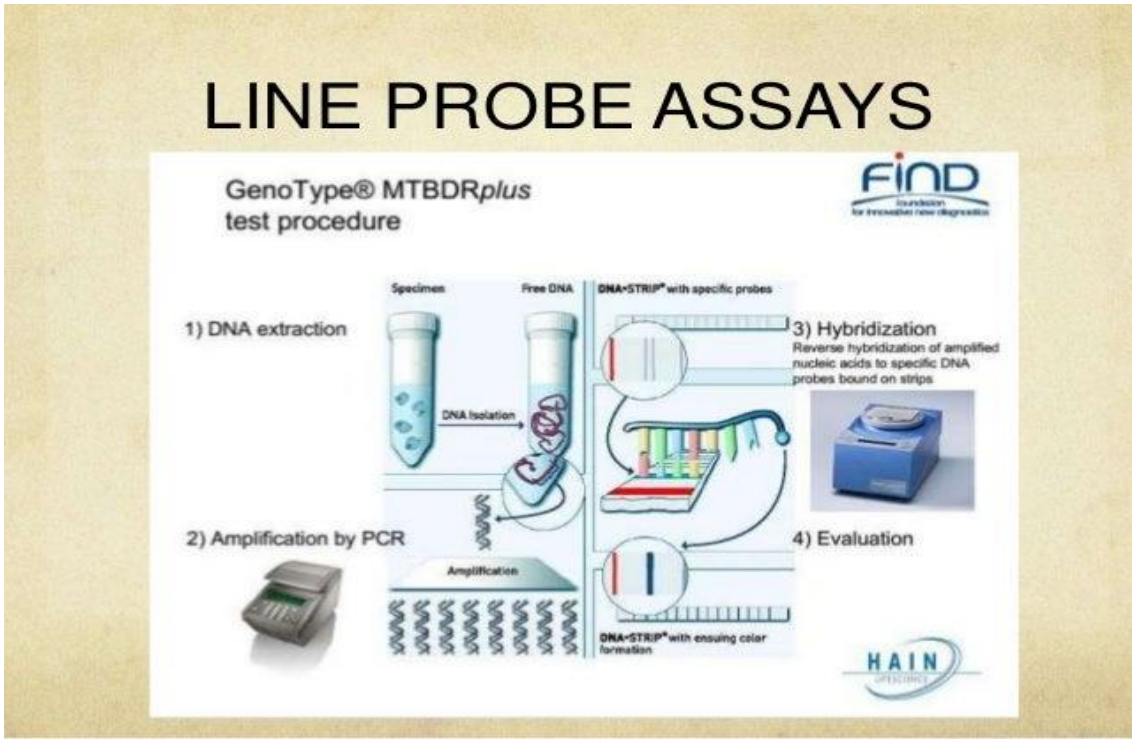
Limitations

Slow growth of MTB: long turn-around time

Expensive equipment

Requires specialised infrastructure and well trained personnel

TB Containment Lab for Liquid culture Intermediate Reference Laboratory (IRL)
Dept of Microbiology, Goa Medical College



TB Diagnostic Laboratory Methods: CBNAAT (GeneXpert)

- Fully automated
- Time-to-result 2 hours (walk away test)
- Closed system (no contamination risk)
- Sensitivity for PTB in adults= 88%

  (98% for smear positive TB, 68% for smear negative TB,

  79% in HIV +ve, 66% in children);
- Specificity = 98%
- Extra pulmonary samples: good yield.
- R-resistance: Sensitivity = 95%;

  Specificity = 98%
- ***Limit of detection (LOD) of 131 CFU/ml sample***

Xpert MTB/XDR

- Detects mutations associated with resistance towards **H, FQ, SLI & Eto in a single test**.
- Results are available in **less than 90 minutes**.

Drug resistance	Target region
Isoniazid	inhA promotor, katG,fabG1, oxyR- ahpC intergenic region
Ethionamide	inhA promotor
Fluoroquinolone	gyrA, gyrB
Amikacin, Kanamycin, Capreomycin	rrs, eis promotor

TRUENAT MTB

- Molbio Diagnostics-Verna,Goa
- Truenat MTB :Sensitivity = 83%
  : Specificity = 99%

  Truenat MTB-RIF:Sensitivity=93%
  : Specificity=95%
- ***LOD-100CFU/ml***
- ***time-to-result- 2 hrs (2 steps)***
- Battery operated, portable
- POC tool to diagnose TB.
- Minimal biosafety requirements.

AFB smear microscopy and Culture

Have limitations, hence these conventional methods, in recent years have been challenged by several new methods and tools

Molecular diagnostics for TB

Activities to strengthen TB diagnosis "Find the missing cases"

- ***Increase the percentage of TB cases confirmed bacteriologically,*** based on scaling up the use of recommended diagnostics that are more sensitive than smear microscopy
- ***The microbiological detection of TB is critical*** because it allows people to be correctly diagnosed and started on the most effective treatment regimen as early as possible.
- ***Most clinical features of TB have low specificity*** which may lead to incorrect diagnosis of TB, and unnecessary TB treatment.

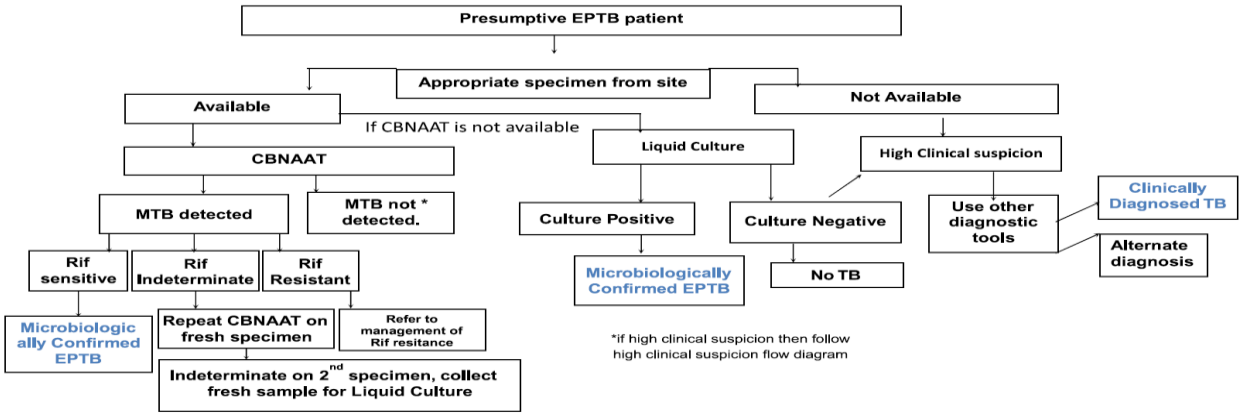
UPFRONT NAAT

- To help in early and accurate diagnosis and in a bid to offer the best available tools for the diagnosis of TB, Goa has moved to UPFRONT NAAT
- Sputum smear microscopy has been replaced by upfront NAAT w.e.f 28th Dec 2020 across the state.

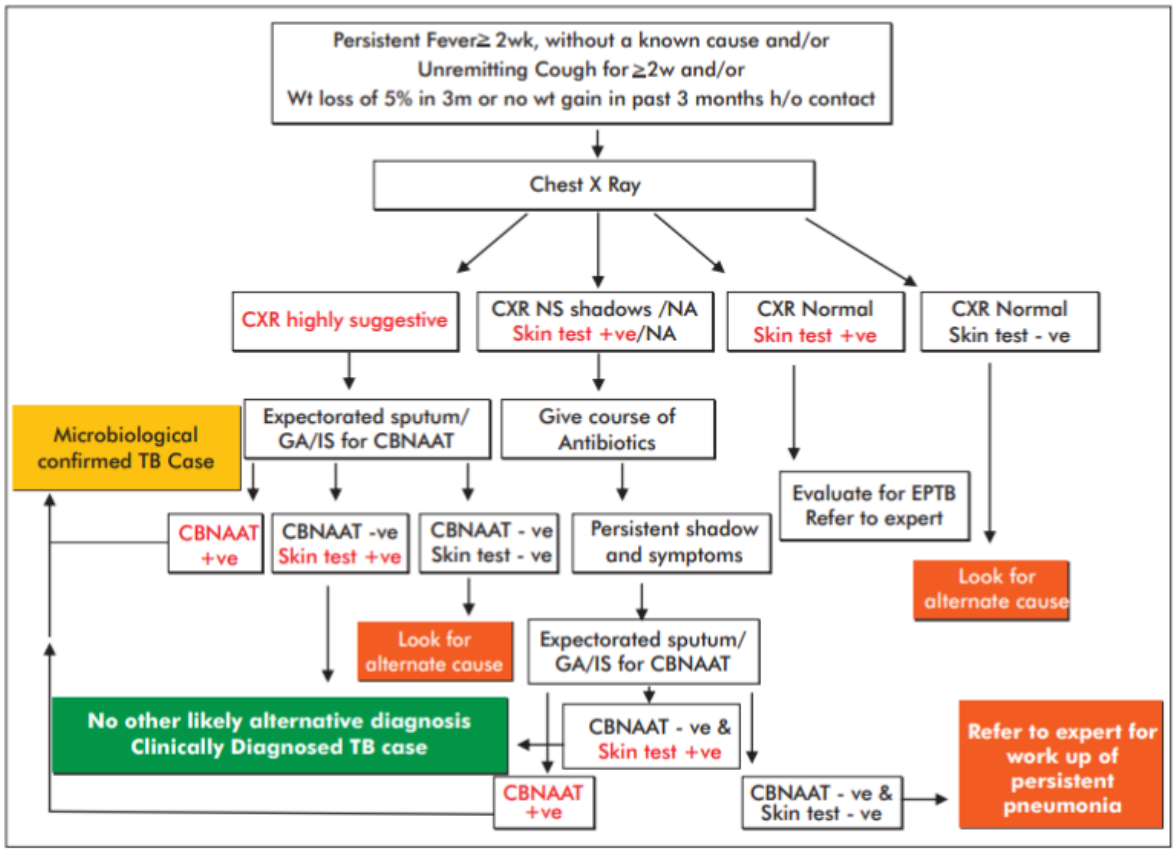
WHO-recommended rapid diagnostics (WRDs)

- COVID-19 has highlighted the central role of diagnostics in the public health response. Health systems should transition from use of outdated diagnostic technologies such as smear microscopy and over-reliance on clinical diagnosis to use of WHO-recommended rapid diagnostics that are highly accurate, reduce the time to diagnosis, improve outcomes that are important to patients and are cost-effective

Diagnostic Algorithm for Extra Pulmonary TB



Diagnostic algorithm for Paediatric Pulmonary Tuberculosis



DR –TB CASE-FINDING

Vision

- To **provide Universal DST** to all notified TB patients: Universal access to rapid DST for at least rifampicin, and further DST for at least fluoroquinolones among all TB patients with rifampicin resistance (preferably before initiation of treatment to maximum within 15 days of diagnosis).
- A staggered testing algorithm utilizing newer rapid diagnostic technologies such as NAAT (CBNAAT/ TrueNat), first and second-line LPA in line with WHO guidelines.

Role Of Microscopy
FOLLOW UP LAB MONITORING OF TB PATIENTS

Sputum smear microscopy at DMC's for pulmonary TB cases.

End IP and End CP

SUMMARY

- Ensure early diagnosis and microbiological confirmation of TB
- Good quality sample = good quality report
- Upfront NAAT is offered for diagnosis of TB in Goa: CBNAAT /TRUENAT-MTB
- NAAT detects:1) MTB & 2) Rifampicin resistance
- FL-LPA offered for RSTB
- LPA and LC-DST offered for RRTB
- A positive NAAT test provides useful confirmation so that TB treatment can be started promptly on the correct regimen. A negative test does not always rule out TB

DIAGNOSIS OF TB INFECTION AND TB PREVENTIVE TREATMENT (TPT)

- Offered to All household contacts of Pulmonary TB

a. If they are symptomatic → investigate for TB and manage appropriately

b. If they are not having any signs/ symptoms of TB →

   i. Age <5 years. Rule out active TB and provide TPT; and

   ii. Age 5 years and more. Rule out active TB and provide TPT if TBI test (IGRA) is positive

Regimen of TPT: 6 months of daily isoniazid mono therapy (6H)