TUBERCULOSIS

AGENT FACTORS

Agent: Mycobacterium tuberculosis

Source of infection:

- Human source – human case positive for tubercle bacilli
- Bovine source – infected milk

Communicability: patients are infective as long as they remain untreated.

HOST FACTORS

- Age: affects all age, predominantly affect 15-24 yrs of age
- Sex: more prevalent in males
- Nutrition: malnutrition predisposes to TB
- Immunity: no inherited immunity but acquired as a result of natural infection or BCG vaccination.

ENVIORNMENTAL FACTORS

- Poor housing, poor ventilation, overcrowding
- Undernutrition, smoking, alcohol abuse
- Lack of education, lack of awareness

MODE OF TRANSMISSION

Droplet infection or droplet nuclei

INCUBATION PERIOD: 3-6 weeks for developing a positive tuberculin test

PULMONARY TUBERCULOSIS

When to suspect TB/ **criteria for diagnosis of TB?**

Cough for 2 weeks or more and other symptoms such as evening rise of temperature, chest pain, loss of weight, loss of appetite, haemoptysis, shortness of breath, history of contact with TB case**.**

PRESUMPTIVE PULMONARY TB

- Cough > 2 weeks
- Fever>2 weeks
- Significant weight loss
- Haemoptysis
- Abnormality in chest radiograph

DIAGNOSIS OF PULMONARY TUBERCULOSIS

Diagnosis of active tuberculosis

Sputum smear microscopy by Acid- fast staining

Specimen collection:

- 2 sputum samples are recommended- spot sample and early morning sample
- Alternatively, 2 spot samples at least one hour apart can be collected.
- Gastric aspirate in children

Ziehl – Neelsen staining technique

- It is positive when there is at least 10,000 bacilli / ml of sputum.
- Slides are graded as negative or positive on the presence of bacilli.
- Mycobacterium appears as long slender, beaded, red colour acid fast bacilli in a positive slide

- Positive smears are further graded as scanty, +1, +2 and +3 based on number of bacilli detected.

Fluorescent Microscopy

Auramine stain used, bacilli appear brilliant green against dark background

Sputum culture

- Solid medium - Lowenstein Jensen media
  Shows rough, tough and buff-coloured colonies in 6-8 weeks
- Automated liquid culture system- BACTEC MGIT 960, Bact/ ALERT- detects growth as well as resistance to anti Tb drugs.

Rapid molecular assays

- Nucleic acid amplification test (NAAT)

CBNAAT (GeneXpert) and Truenat-for identification and detection of resistance to rifampicin; has a turnaround time 2 hours

- Line probe assay (e.g. Genotype TB) -for identification and detection of resistance to 1st and 2nd line ATDs; has a turnaround time of 2-3 days.

Chest X ray

- For diagnosis of smear negative pulmonary Tb and Tb in children
- For diagnosis of pleural and pericardial effusion, miliary tb

Diagnosis of latent tuberculosis

Tuberculin skin test /Mantoux test

0.1 ml of purified protein derivative is administered on the flexor aspect of the fore arm

After 48- 72 hours and induration surrounded by erythema is produced.

≥10 mm: positive

6-9mm: Doubtful

< 5mm: negative

- In adults positive TST indicates present or past exposure
- In children, positive test indicates active infection
- False positive: BCG vaccination, nontuberculous mycobacterium infection
- False negative: HIV, malnutrition, transplant patients

Interferon Gamma Release Assay (IGRA)

Sensitized T lymphocytes collected from suspected individuals and exposed to specific antigens release high levels of IFN gamma

ANTITUBERCULAR DRUGS

First-line agents for DS-TB

• Isoniazid (H)

• Rifampicin (or Rifampin) (R)

• Pyrazinamide (Z)

• Ethambutol (E)

Second-line agents for DR-TB

A	Fluoroquinolones: • Ciprofloxacin, • Levofloxacin (Lfx) or • Moxifloxacin (Mfx)
	Linezolid (Lzd)
	Bedaquiline (Bdq)
B	Clofazimine (Cfz)
	Cycloserine (Cs)
C	Amikacin (Am) or Streptomycin (S)
	Ethionamide or Prothionamide (Eto/Pto)
	p-amino salicylic acid (PAS)
	Imipenem (Ipm) or Meropenem (Mpm)
	Delamanid (Dlm) or Pretomanid (Ptm)

MANAGEMENT OF DRUG SENSITIVE TUBERCULOSIS

Pre-treatment counselling

- Counsel his / her family members about mode of spread, treatment duration, dosage schedule, common drug side effects and methods to prevent them
- Importance of regular treatment and consequence of irregular treatment
- Screening of comorbidities.

Pretreatment evaluation

1. Detailed history and examination
2. Weight and height.
4. Blood sugar
3. Complete blood count.
5. Liver function test.
6. Blood urea and creatinine
7. Urine examination
8. Chest X-ray
9. Pregnancy test (for all women in child bearing age group)
10. HIV testing

Drug regime

Drug regime - 2HRZE plus 4 HRE

H = Isoniazid 10 mg/kg/day in adults

R = Rifampicin 15 mg/kg/day in adults

Z = Pyrazinamide 35 mg/kg/day in adults

E = Ethambutol 20 mg/kg/day in adults

- Intensive phase (IP) consists of 2 months with four drugs HRZE
- Continuation phase (CP), consists of 4 months with three drugs HRE
- Drugs are available as Fixed dose combinations as per appropriate weight bands.
- FDC should be taken orally, once in a day.

Daily dose schedule for adults as per weight bands

Weight category	No. of tablets in IP	No. of tablets in CP
25-34 kg	**2**	**2**
35-49 kg	**3**	**3**
50-64 kg	**4**	**4**
65-75 kg	**5**	**5**
≥75	**6**	**6**

Nikshay entry: It is a web portal introduced for surveillance of Tb. once the treatment regimen is finalised, the govt of India made it mandatory for all health care providers to notify all new Tb cases through the web.

Follow-up of the treatment

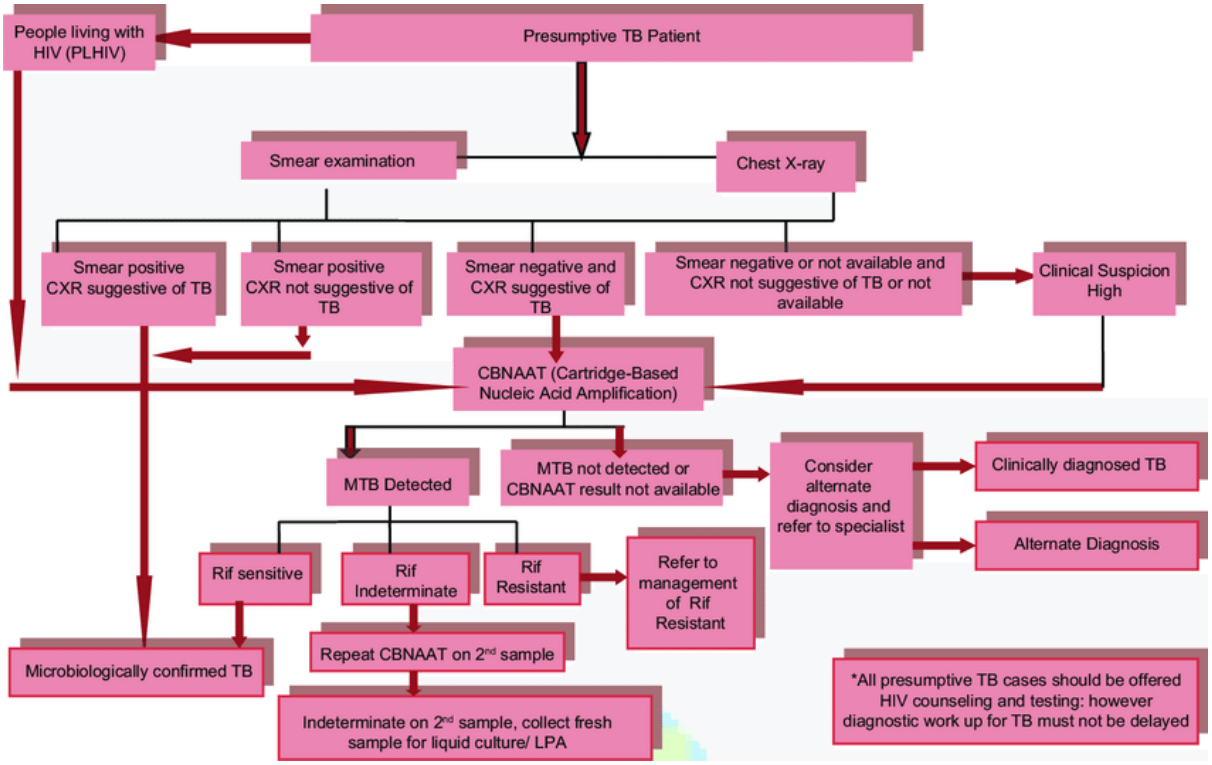
a. *Clinical follow up*: It should be done at a monthly interval.

b. *Laboratory investigations*: Sputum smear microscopy should be done at the end of intensive phase and end of treatment.

If the sputum result is positive at the end of IP, then CP will be initiated and continued till DST results are available.

c.*Long term follow-up* at the end of 6, 12, 18, and 24 months should be done.

In presence of any symptoms, sputum microscopy and culture are considered.



DRUG RESISTANT TB

- Monoresistance: Resistance to one first line anti-Tb drug
- Polydrug resistance: Resistance to more than one first line anti-TB drug (other than both isoniazid and rifampicin)
- Multidrug resistance: Resistance to both isoniazid and rifampicin with or without resistance to other first line drugs.
- Extensive drug resistance: Resistance to any Fluoroquinolones and at least one of 3 second line Injectable drugs.

How do detect drug resistance TB?

- Molecular diagnosis like CBNAAT & Line probe assay (LPA)
- Liquid culture and drug sensitivity testing (LC-DST)
- Solid culture and drug sensitivity testing

Management of DR-TB

Pre-treatment evaluation

All patient should be evaluated by

- Detailed history, previous history of ATT,
- General and systemic examination,
- CBC, FBS/PPBS, RFT, LFT, Thyroid function test, HIV testing
- Urine examination (routine and microscopy), Urine Pregnancy Test
- Chest X-ray
- ECG
- Psychiatric evaluation and surgical evaluation.

Counsel and referral:

- Counsel his / her family members about mode of spread, treatment duration, dosage schedule, common drug side effects and methods to prevent them
- Importance of regular treatment and consequence of irregular treatment
- Screening of comorbidities.
- Patients should also be referred to HIV testing centres.

Treatment regimens

H mono/poly DR TB (R resistance not detected and H resistance detected)

All oral H mono/poly DR TB regimen:

(6 or 9) Lfz R E Z

Treatment duration of 6 months extended to 9 months in certain conditions like patients with extensive disease, uncontrolled comorbidity, extrapulmonary TB , if smear is positive at the end of 4th month.

No separate IP or CP

MDR/RR TB

Shorter oral Bedaquiline containing MDR/RR TB

- Initial phase of 4 months that may be extended up to 6 months
- Continuation phase of 5 months
- Total duration of 9-11 months.
- Bdq is used for a duration of 6 months.

IP: (4-6) Bdq (6m), Lfx, Cfz, Z, E, H, Eto

CP: (5) Lfx, Cfz, Z, E

Shorter injectable containing regimen

The regimen composition and duration is as follows:

IP: (4-6) Mfx^{h}, Km/Am, Eto, Cfz, Z, H_{h}, E

CP: (5) Mfx, Cfz, Z, E

All oral longer M/XDR TB regimen

(18-20) Bdq (6 month or longer) Lfx Lzd Cfz. Cs

Note: Lfx-Levofloxacin; Mfx - Moxifloxacin; Km - Kanamycin; Am - Amikacin; Eto - Ethionamide, Cfz-Clofazimine; Bdq-Bedaquiline; Lzd-Linezolid; Cs - Cycloserine

PAEDIATRIC TB

Diagnosis of childhood TB

By clinical evaluation and laboratory investigations

Medical history includes

- Clinical features and its duration (persistent symptoms like fever since 2 weeks, cough since 2 weeks, weight loss of 5% in 3 months, no weight gain for last 3 months)

- Family history of contact with TB

Perform diagnostic test

- Tuberculin skin test
- Chest radiography
- CBNAAT is preferred investigation of choice.
- Smear microscopy can be performed with sputum or non-respiratory specimens.

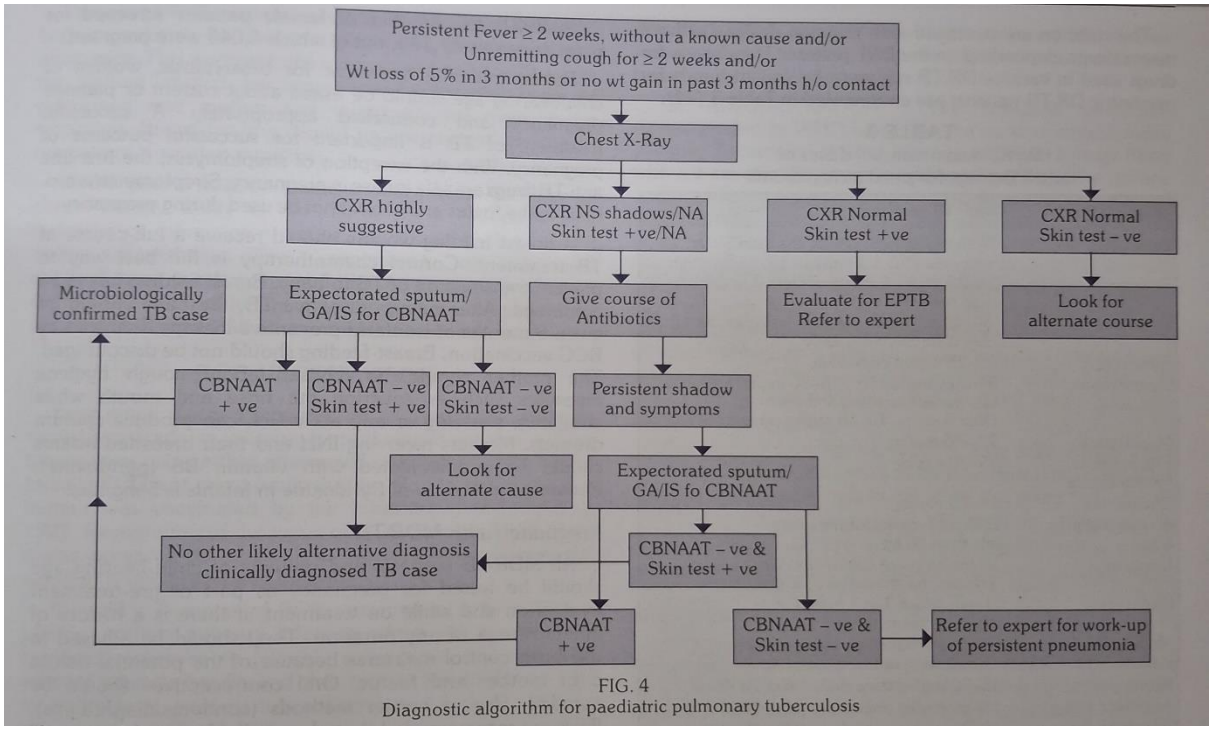


FIG. 4
Diagnostic algorithm for paediatric pulmonary tuberculosis

Treatment of paediatric TB

Dispersible FDC, flavoured

- Rifampicin 75mg + Isoniazid 50 mg + Pyrazinamide 150mg
- Rifampicin 75mg + Isoniazid 50 mg

Dispersible Loose drugs

- Ethambutol 100mg
- Isoniazid 100mg

Intensive phase	Rifampicin 75mg + Isoniazid 50 mg + Pyrazinamide 150mg	Ethambutol 100mg
Continuation phase	Rifampicin 75mg + Isoniazid 50 mg	Ethambutol 100mg

Paediatric TB to be treated under NTEP in daily dosages as per 6 weight bands.

Weight	Number of tablets			
	IP		CP	
	HRZ	E	HR	E
4-7 kg	1	1	1	1
8-11 kg	2	2	2	2
12-15 kg	3	3	3	3
16-24 kg	4	4	4	4
25-29 kg	3 + 1A	3	3 + 1A	3
30-39 kg	2 + 2A	2	2 + 2A	2

A = Adult FDC

For children weighing more than 39 kg use adult weight bands.

If the paediatric contact is tested negative, what are the next steps to be taken?

- Tb preventive therapy should be taken
- For age < 10 years chemoprophylaxis with isoniazid monotherapy i.e., 10 mg/kg administered daily for 6 months.

TUBERCULOSIS AND HIV CO-INFECTION

Q)AIDS is reviving the old problem of tuberculosis

- Immunosuppression - AIDS makes the patient more vulnerable to infections like Tuberculosis
- TB reactivation- latent TB infection can become Active in people with HIV
- Co-infection complicates the management of both the disease
- Regions with high prevalence of HIV often face dual burden of both disease

Epidemiological impact

- Reactivation of latent infection
- Primary infection: New tb infection in people with HIV can progress to active disease quickly
- Recuring TB infection in an already cured TB individual
- In the community: more new case of active tuberculosis leads to more death in community

Q) A truck driver with HIV may have developed tuberculosis chest. What problems do you anticipate in the diagnosis and management of the case.

Sputum smear microscopy is the mainstay for tuberculosis diagnosis. But in advance HIV infection, standard diagnostic tools can be more difficult because of

- Higher frequency of negative sputum smears. Sputum culture is needed to confirm diagnosis.

- Tuberculin skin test being more likely to be negative because of decreased immunity in HIV patients. There is high frequency of false negative tuberculin skin test.
- Atypical presentations in chest radiography. In individuals with weakened immune systems there is less tissue destruction and less cavitation.
- HIV infected individuals are more likely to develop extra-pulmonary tuberculosis.
- Co-infection complicates the management of both the disease
- Adverse events are more common
- Rigorous monitoring is required to ensure adherence to treatment, early detection and treatment of adverse events

TRAETMENT

- Among HIV infected persons , treatment of TB is the same as that in HIV negative TB patients.
- Start anti-tuberculosis treatment first and then start ART as soon as TB treatment is tolerated.
- If drug resistance TB patients on second line ART, Rifampicin should be replaced with Rifabutin.
- In addition to TB treatment, all HIV infected TB patients must be provided with co-trimoxazole preventive therapy to prevent opportunistic infections
- In order to prevent the incident of TB in HIV infected individuals' isoniazid preventive therapy is recommended
- Adult and adolescents – Isoniazid 300 mg + pyridoxine 50 mg per day for 6 months
- Children above 12 months - Isoniazid 10mg/kg + pyridoxine 25 mg per day for 6 months

EPIDEMIOLOGICAL INDICES TO MEASURE TB

Incidence of infection (Annual Infection Rate/Annual risk of Infection)

- Percentage of population under study who will be newly infected by Mycobacterium tuberculosis among the non-infected population during the course of one year

Prevalence of infection

- Percentage of individuals who show a positive reaction to the standard tuberculin test

Incidence of cases

- Number of new and recurrent (relapse) episodes of TB occurring in a given year

Prevalence of disease or case rate

- Number of all TB cases at a given point in time

Mortality rate (in HIV negative people)

- Number of deaths caused by TB in HIV negative individuals

Case fatality rate

- Number of deaths among people with active TB disease

Case notification rate

- New and recurrent episodes of TB notified in a given year

Case detection rate: Number of new and recurrent cases of TB in a year divided by the estimated incidence of such cases in the same year

Advices to family in case of TB

- Practice good hygiene, use masks & avoid close contact during infectious period
- Ensure proper ventilation in the patient's room to prevent transmission

- Educate the family about tuberculosis myths and to reduce stigma.
- Ensure treatment adherence of patients and attend follow ups
- Advice screening for tuberculosis by all family members
- Educate about proper disposal of sputum
- BCG vaccination to family members especially children
- Communication with health care provider

NATIONAL TUBERCULOSIS ELIMINATION PROGRAMME

OBJECTIVES

- To achieve 90% notification rates for all population.
- To achieve 90% success rate for all new and 85% for all retreatment cases.
- To significantly improve the successful outcomes of treatment of DR-TB cases.
- To achieve decreased morbidity and mortality of HIV associated TB.
- To improve outcomes of TB care in private sector.

STRATEGIES

DOTS Strategy

Directly Observed Treatment Short-course (DOTS) strategy adopted by Revised National TB Control Programme as cost-effective approach to revitalize the TB control programme in India.

- Under DOTS strategy, anti-tuberculosis medications are swallowed by patients under Supervision of a health worker, thereby ensuring that proper medication are given at proper intervals at right dose
- DOTS increases the accuracy of diagnosis of tuberculosis by advocating sputum smear microscopy, which reduces the spread of disease

- Free medications are provided and the duration of illness is reduced
- Social stigma associated with DOTS is reduced which encourage symptomatic persons to seek medical care

DOTS plus regimen comprises 6 drugs

- Pyrazinamide
- Ethambutol
- Ofloxacin
- Ethionamide
- PAS/Cycloserine
- Kanamycin

It consists of 5 components

- ***Political will and administrative commitment***.

A well-functioning DOTS programme

Long term investment of staff and resources

Addressing the factors leading to emergence of MDR TB

- ***Diagnosis by quality assured sputum smear microscopy***.

Proper triage for patients for culture and drug susceptibility testing and management under DOTS plus

Coordination with national and supra national reference laboratories

- Adequate supply of quality assured short course chemotherapy drugs.
- Directly observed treatment ensuring long term adherence
- Systematic monitoring and accountability.

STOP TB Strategy

In 2006, STOP TB strategy was announced by WHO and adopted by RNTCP

The components are as follows:

- Pursuing quality DOTS-expansion and enhancement.
- Addressing TB/HIV and MDR-TB.
- Contributing to health system strengthening.
- Engaging all care providers.
- Empowering patients and communities.
- Enabling and promoting research (diagnosis, treatment, vaccine).

End TB Strategy

- In 2014, the World Health Assembly unanimously approved to end global TB epidemic by "End TB Strategy", a 20-year programme with vision of a world with zero death, disease and suffering due to TB.
- The programme has been renamed from Revised National Tuberculosis Control Programme (RNTCP) to National Tuberculosis Elimination Programme (NTEP).

Components

- Integrated, patient-centred care and prevention.
- Bold policies and supportive systems.
- Intensified research and innovation.

Indicators	Milestones		Targets	
	2020	2025	SDG 2030	END TB 2035
Reduction in number of TB death	35%	75%	90%	95%

compared to 2015				
Reduction in TB incidence rate compared with 2015	20%	50%	80%	90%
TB affected families facing catastrophic costs due to TB	0%	0%	0%	0%

NATIONAL STRATEGIC PLAN (NSP) 2017-2025

The VISION is TB free India with zero deaths, disease and poverty due to TB

The key strategies are as follows:

- Private sector engagement
- Active case finding
- Drug resistant TB case management
- Addressing social determinants including nutrition
- Robust surveillance system
- Community engagement and multi-sectoral approach

Expected outcome:

The aim of the National Strategic Plan is to achieve elimination of TB by 2025.

- 80% reduction in TB
- 90% reduction in TB mortality
- 0% patient having catastrophic expenditure due to TB

When will you state that, control of TB is achieved?

Reduce the incidence to less than 1 case per 1000000 population.