Special Correspondence

[We are publishing this Special Correspondence to commemotare World TB Day on 24th March]

National Tuberculosis Elimination Programme : New Guidelines for Management of Drug Sensitive TB

Swapnendu Misra[1], Papia Mondal[2], Jaydip Deb[3], Rama Saha[4]

India has largest number of tuberculosis patients in the world. India accounts for 27% of global TB burden[1]. India has highest burden of both TB and MDR TB and second highest of HIV associated TB[2]. 2.69 million incident TB cases emerged in India in 2018. Incidence of HIV TB and pediatric TB was 92000 and 342000 respectively. MDR TB incidence was 130000 contributing to 24% of global MDR TB burden. Moreover any drug resistance among new patients is 22.54%, among previously treated patients is 36.82% and among all patients 28.02% . This is a very alarming situation. TB kills more adults in India than any other infectious disease.In India every day more than 6000 develop TB disease, more than 600 people die of TB (ie, 2 deaths every 5 minutes).

Revised national tuberculosis control programme (RNTCP) was launched in India in 1993. In 2006 entire country was covered by RNTCP. World health organization (WHO) started stop TB strategy in 2006. WHO adopted End TB Strategy in 2020.Vision is a world free of TB and zero death, disease, suffering due to TB. Goal is to end the global TB epidemic. Government of India preponed END TB Strategy by 2025, 5 years ahead of global target. Indian target by 2025 is to reduce TB incidence, prevalence and mortality per lakh population to 44, 65 and 3 respectively. It is to be ensured that no family should suffer catastrophic costs due to TB. In this scenario National Strategic Plan 2017-2025 has been implemented and it is built on 4 pillars '**DETECT-TREAT-PREVENT-BUILD**'. Activities under the plan are :

- Active TB case finding
- Latent TB infection (LTBI) management in high risk population
- Newer and shorter regimen
- Private sector engagement
- Preventive and awareness measures
- Financial/Nutritional support to patients
- IT enabled surveillance

Now the new goal is not to control TB but to eliminate TB. In this context Revised National TB Control Programme (**RNTCP**) nomenclature has been changed to National TB Elimination Programme (**NTEP**) from January 2020.

Nodal point of NTEP is tuberculosis unit(TU). It is situated at sub district level. In urban areas 1 TU per 2,00,000 population.TU will have one designated microscopy centre (DMC) for every 1 lakh population (50,000 in tribal, desert, remote and hilly region).Microscopy centres are also located in medicalcolleges, corporate hospitals, ESI, railways, NGOs, private hospitals.

Presumptive pulmonary TB is defined as any patient with cough for more 2 weeks, fever for more 2 weeks , significant weight loss, hemoptysis or any abnormality in chest radiograph. Contacts of microbiologically confirmed TB patients, patients living with HIV AIDS (PLHIV), diabetics, malnourished, cancer patients, patients on immune suppressants or steroids should be regularly screened for signs and symptoms of TB. Presumptive extra pulmonary TB is defined as organ specific symptoms and signs like swelling of lymph node, pain and swelling in joints, neck stiffness, disorientation and constitutional symptoms like significant weight loss, persistent fever for more than 2 weeks, night sweats. Presumptive pediatric TB is defined as persistent fever more than 2 weeks or cough more than 2 weeks or loss of weight / no weight gain and history of contact with infectious TB case. Loss of weight is defined as loss of more than 5% body weight as compared to highest weight recorded in last 3 months.

Microbiologically confirmed TB caseis defined as biological specimen positive for AFB or positive for Mycobacterium tuberculosis on culture or positive for tuberculosis through quality assured rapid diagnostic molecular test. Clinically diagnosed TB case is defined as presumptive TB patients who is not microbiologically confirmed but diagnosed with a active TB by a clinician on the basis of X-ray abnormalities, histopathology or clinical signs with a decision to treat the patient with a full course of anti tubercular drugs (ATD). There are some changes in nomenclature of cases. Previously patients defined as relapse now defined as recurrent TB cases. Similarly previously called failure cases now called treatment after failure (Figs 1&2).

Department of Respiratory Medicine, NRS Medical College, Kolkata 700014

[1]MBBS, MD, Assistant Professor

[2]MBBS, Postgraduate Trainee

[3]MBBS, MD, Professor and Head

[4]MBBS, MD, Associate Professor, Department of Pathology, IPGME&R, Kolkata 700020 and Corresponding author

Received on : 23/02/2021

Accepted on : 27/02/2021

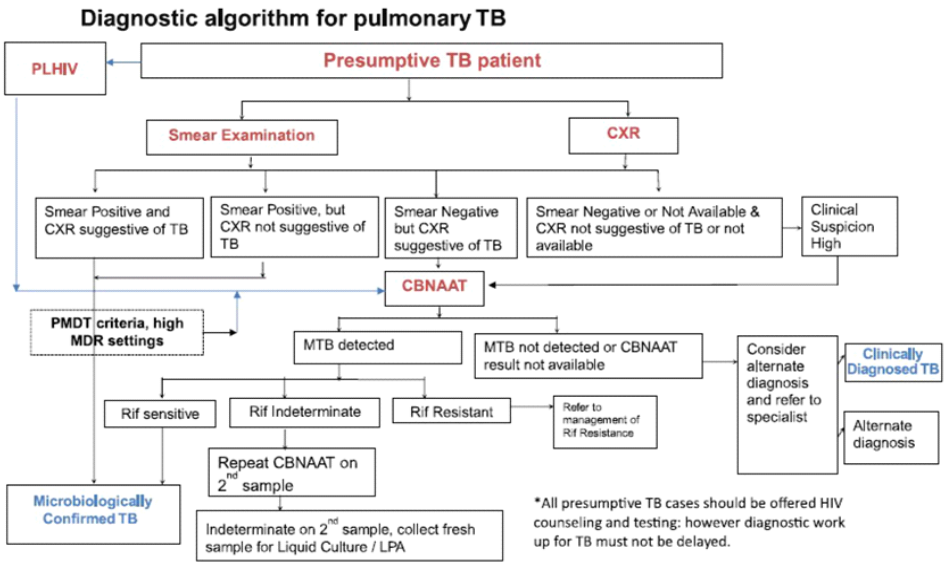

Fig 1 — Diagnostic algorithm for Pulmonary TB

In the diagnosis more emphasis has been given on microbiological confirmation of cases with universal drug sensitivity test (U-DST). NTEP is committed to provide UDST for all notified TB patients (bacteriologically confirmed and clinically diagnosed).DST to be done for at least Rifampicin through rapid molecular test.DST for Isoniazide offered through first line line probe assay (LPA). Cascading DST for fluroquinolone and second line injectable are offered through second line LPA.

Diagnostic tools for microbiolocal confirmation are sputum smear microscopy (ZN stain, Fluroscent stain), culture (solid LJ media, liquid culture system) and rapid molecular diagnostic tests (CBNAAT, Tru NAAT, Ultra NAAT). For culture at present liquid culture like mycobacterium growth indicatorTube (MGIT) is commonly used. Facility of liquid culture now available through NTEP lab network and other accredited laboratories.Under current universal DST strategy specimens like induced sputum, gastric aspirate, bronchoalveolar lavage fluid may be used for upfront rapid molecular tests or for liquid culture if rapid molecular tests are negative.

Among rapid molecular tests, ultra NAAT has lower detection limit (16 bacilli per ml sputum) as compared to 131 per ml for CBNAAT.It isspecially useful for paucibacillary disease, children andforHIV TB-coinfection.Ultra NAAT may replace CBNAAT in near future (Fig 3).

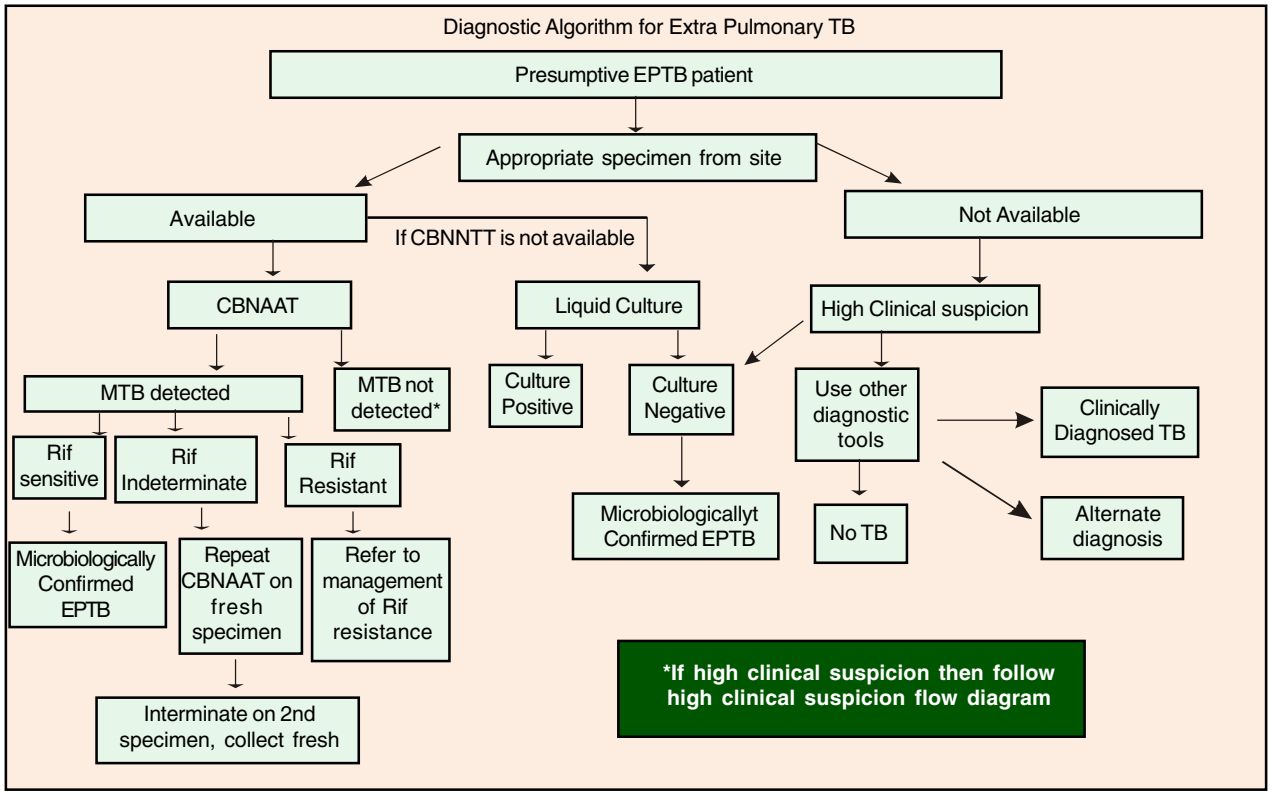

Fig 2 — Diagnostic algorithm for Extra Pulmonary TB

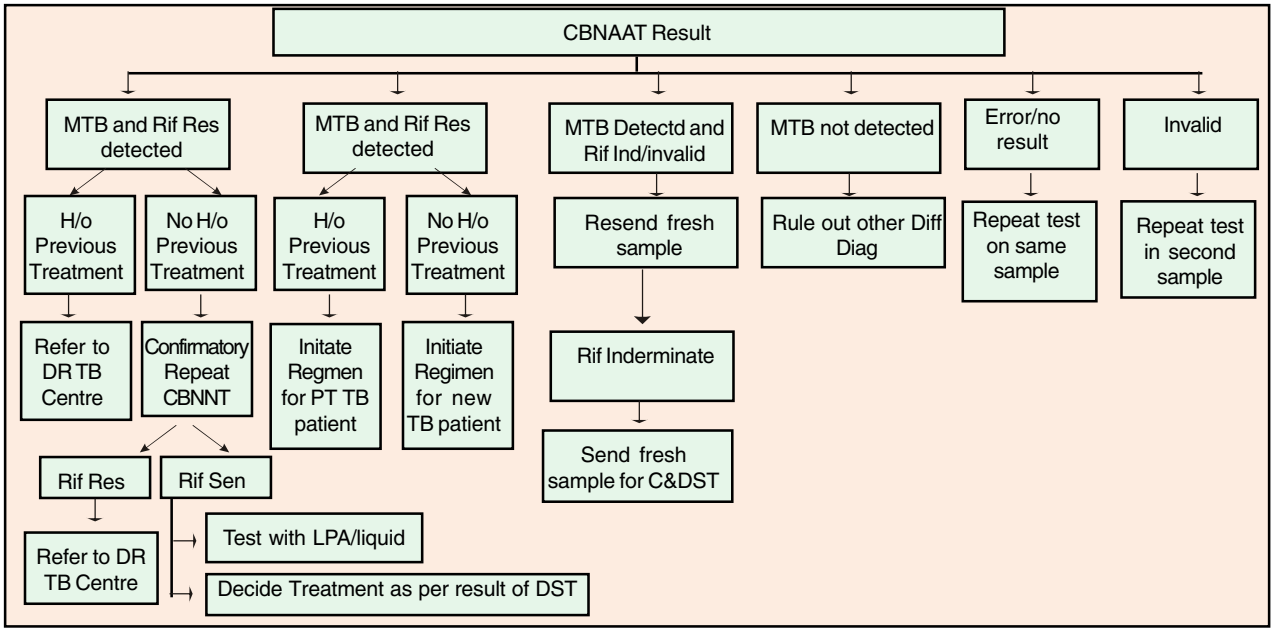

Fig 3 — CBNAAT result algorithm

Two newer diagnostic tools have been developed. Lateral flow urine lipoarabinomannan (LF-LAM) assayused for diagnosis of TB in HIV positive patients with signs and symptoms of TB(pulmonary and/or extra-pulmonary) who have a CD4 cell count less than or equal to 100 cells/μL. C-TB is a next-generation skin test with high specificity. It contains the same antigens used in IGRA ie, ESTA 6 & CFP 10. It is unaffected by BCG vaccination status and very useful for latent TB diagnosis.

In pediatric patients also every effort should be made for microbiological diagnosis. As per NTEP guidelines, diagnosis of non tubercular mycobacteria (NTM) should be done using a mix of diagnostic technologies.

Goals and objectives of treatment are render patient non-infectious, break the chain of transmission, decrease pool of infection, decrease case fatality and morbidity, ensuring relapse free cure, minimize and prevent development of drug resistance.The principal of treatment of drug sensitive tuberculosis (other than DR-TB) is with daily regimen with daily fixed dose combination of first line antitubercular drugs in appropriate weight bands. Changes from past guideline are:

- Daily regimen.
- Fixed dose combination drugs (FDC).
- New weight band.
- Ethambutol in Cat-I continuation phase (CP).
- No extension of intensive phase (IP).
- No Cat-II regimen.

Intermittent regimen changed to daily regimen because relapse rate with intermittent regimen is as high as 8.8%[3] and 12.3%[4] as evidenced by two separate studies whereas internationally acceptable relapse rate is less than 5%. FDC drugs are given because of simplicity of treatment, increased patient acceptance (fewer tablets to swallow, prevents concealed irregularity), increased health worker compliance (fewer tablets to handle),easier drug management, reduced use of monotherapy and lower risk of emergence of drug resistance.

In India pre treatment INH resistance is high[5]. Pre-treatment INH resistance lead to amplification of acquired rifampicin resistance, leading tomulti drug resistance (MDR). Ethambutol now included in CP because it will protect Rifampicin and prevent emergence of MDR TB.

In previous weight band dose of ATD for weight band 30 to 40 kg was inappropriately high. It was leading to drug toxicity and default. In NTEP guidelines weight band has been revised into 5 weight categories.

The revised weight band for standard first line regimen for TB in adults (Fig 4).

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

Fig 4 — The revised weight band for standard first line regimen for TB in adults

To initiate treatment, new and previously treated drug sensitive TB will be given "Regimen for new patients"-2 months intensive phase with Isoniazide, Rifampicin, Ethambutol, Pyrazinamide and 4 months continuation phase with Isoniazide, Rifampicin, Ehambutol. For new and previously treated drug resistant TB regimen will be based on DST pattern. Systemicsteroids given as adjunctive therapy in TB Pericarditis & Meningeal TB. For CNS TB, skeletal TB, disseminated TB continuation phase may be extended by 12 to 24 weeks.

Follow up of treatment should be both clinical and laboratory follow up. At the end of 2 months if sputum smear is positive, there is no provision of extension of intensive phase. Sample to be sent for rapid molecular test or liquid culture and regimen will be based on DST pattern. Long term follow up is a new inclusion in guideline. After completion of treatment, patients should be followed up at the end of 6,12,18 and 24 months. It will help to detect recurrence of TB at the earliest. Pyridoxine is not required for all TB patients. To prevent INH related neuropathy it should be given in persons at high risk of Vitamin B6 deficiency like alcoholics, malnourished persons,pregnant and lactating women,patients with conditions such as chronic renal failure, diabetes and HIV infection.

In HIV infected patients, active case finding to be done. Treatment of TB and HIV should be done from a single window.

INH preventive therapyto be given to children less than 6 years who are close contacts of drug sensitive TB patient irrespective of BCG vaccination/nutritional status. Active TB must be excluded. Dose is 10mg per kg body weight for 6 months. Additional indications for IPT are HIV infected children known exposure to infectious TB case or TST positive (≥5mm induration) ,all TST positive children receiving immunosuppressive therapy (eg, Childrenwith nephrotic syndrome, acute leukaemia, etc), children born to mother diagnosed with TB in pregnancy (Give BCG at birth) and adults & adolescents living with HIV.

Latent TB is defined as presence of mycobacterium tuberculosis in the body without signs and symptoms or radiographic or bacteriologic evidence of tuberculosis disease. It is considered as a state of persistent immune response to stimulation by M. tuberculosis antigens. In India 35 to 40% population have latent TB. Latent TB patients has 10% lifetime risk of active TB. Risk is 16 to 21 times higher in HIV infected persons.As it is not possible to treat all patients with latent TB, eligible patients who should receive latent TB treatment are people living with HIV, infants less than 12 months in contact with active TB, household contacts of pulmonary TB, children/adult on immunosuppressive therapy (Fig 5).

99 DOTS has been implemented in the new guideline for accurate treatment monitoring at very low cost. Patients take medicines based on weight band and calls a toll free number.

Recommended dosages of Drugs for the Treatment of LTBI

Drug Regimen	Dose per kg body weight	Maximum dose
Isoniazed alone, daily for 6 or 9 months	Adults, 5 mg Children, 10 mg (range, 7-15 mg)	300 mg
Daily rifampicin alone for 3-4 months	**Adults, 10 mg Children, 15 mg (range, 10-20 mg)**	**600 mg**
Daily isoniazid plus rifampicin for 3-4 months	Isoniazid : Adults, 5 mg Children, 10 mg (range, 7-15 mg) Children, 15 mg (range, 10-20 mg)	Isoinazid, 300 mg Rifampicin, 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Individuals aged 12 years; Isoniazid : 15 mg Individuals aged : 2-11 years: Isoniazid : 25 mg Rifapentine: 10.0-14.0 kg = 300 mg 14.1-25.0 kg = 450 mg 25.1-32.0 kg = 600 mg 32.1-50.0 kg = 750 mg >50 kg = 900 mg	Isoniazid, 900 mg Rifapentine, 900 mg

Fig 5 — Recommended dosages of drugs for the treatment of LTBI

Benefits are focused and more efficient care and accurate reporting.

Nikshay is an Integrated ICT(Information Communication Technology) system for TB patient management and care in India.It is real-time, case-based, web-based surveillance tool. Nikshayaushadhi which is a software for supply chain management of ATD and laboratory consumables has been launched recently.NikshayPoshan Yojana provides nutritional support through direct benefit transfer of 500 INR per month. It is given for all patients on TBtreatment throughout duration of treatment.

References

1 WHO report 2019.
2 NTEP status report 2020.
3 Dave P, Rade K, Modi B, Solanki R, Patel P, Shah A, *et al* — Assessment of long term outcome among new smear positive tuberculosis patients treated with intermittent regimen under Revised National Tuberculosis Control Program, India- A retrospective cohort study. *National Journal of Community Medicine* 2013; **4(2):** 189-94.
4 Thomas A, Gopi PG, Santha T, Chandrasekaran V, Subramani R, Selvakumar N, *et al* — Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. *International Journal of Tuberculosis and Lung Diseases* 2005; **9(5):** 556-61.
5 Swaminathan S, Narendran G, Venkatesan P, Iliayas S, Santhanakrishnan R, Menon PA, *et al* — Efûcacy of a 6-month versus 9-month Intermittent Treatment Regimen in HIV-infected Patients with Tuberculosis. A Randomized Clinical Trial. *American Journal of Respiratory and Critical Care Medicine* 2010; **181(7):** 743-51.