What Is New in the Management of Childhood Tuberculosis in 2020?

VARINDER SINGH[1] AND ANKIT PARAKH[2]

From [1]Department of Pediatrics, Lady Hardinge Medical College and Kalawati Saran Children's Hospital; and [2]Pediatric Pulmonology and Sleep Medicine, BL Kapur Memorial Hospital; New Delhi, India.

Correspondence to: Dr Varinder Singh, Director-Professor, Department of Pediatrics, Lady Hardinge Medical College and Kalawati Saran Children's Hospital, New Delhi 110 001, India. 4vsingh@gmail.com

The Government of India has developed a National Strategic Plan for tuberculosis (TB) elimination by 2025, five years ahead of the global target set by the World Health Organization (WHO). For achieving these targets there has been a paradigm shift in the diagnostic and treatment strategies of TB at all ages. This update summarizes the specific changes in pediatric TB management in light of the guidelines developed by National Tuberculosis Elimination Program and Indian of Academy of Pediatrics.

Keywords: *Diagnosis, End TB strategy, National strategic plan, National Tuberculosis Elimination Program.*

World Health Organization (WHO) announced the End TB strategy with the target of reducing tuberculosis (TB) deaths by 90% and 95%, and, incidence by 80% and 90%, by 2030 and 2035, respectively [1]. However, Government of India has decided to aim TB elimination from our country by 2025, ahead of the global target [2]. Childhood TB is an important area of intervention while drawing the road-map to end TB. National Tuberculosis Elimination Program (NTEP) and Indian of Academy of Pediatrics (IAP) have partnered to develop updated guidelines and training program for management of childhood TB in the country. The salient updates are detailed below.

NEW PARADIGM OF TB DIAGNOSIS

There is a paradigm shift in diagnostic strategy from conventional smear microscopy to molecular methods of diagnosis due to their higher sensitivity. NTEP approved rapid nucleic acid amplification tests (NAAT) like Xpert Rif/Truenat have made it possible to detect *Mycobacterium tuberculosis* (MTb) with much higher sensitivity as compared to smear and rapidity than culture. The testing turnaround time for rapid NAAT is 2 hours. These tests are also nested for establishing rifampicin resistance - a surrogate for multi-drug resistant (MDR) TB.

In addition, NTEP also recommends Line probe assays (LPA) – which are multiplex NAAT- to test for resistance to rifampicin, isoniazid and other second line drugs (flouroquinolones and second line injectables). Unlike rapid NAAT, LPA due to its relatively lower sensitivity can be used directly only in smear positive specimens or else after isolating MTb on culture, and has a turnaround time of 3-4 days.

So, TB diagnostics have now graduated to upfront testing every likely patient for presence of MTb as well as rifampicin resistance under the strategy called universal drug sensitivity testing (U-DST) [3].

How Does It Impact the Diagnosis of TB in Children?

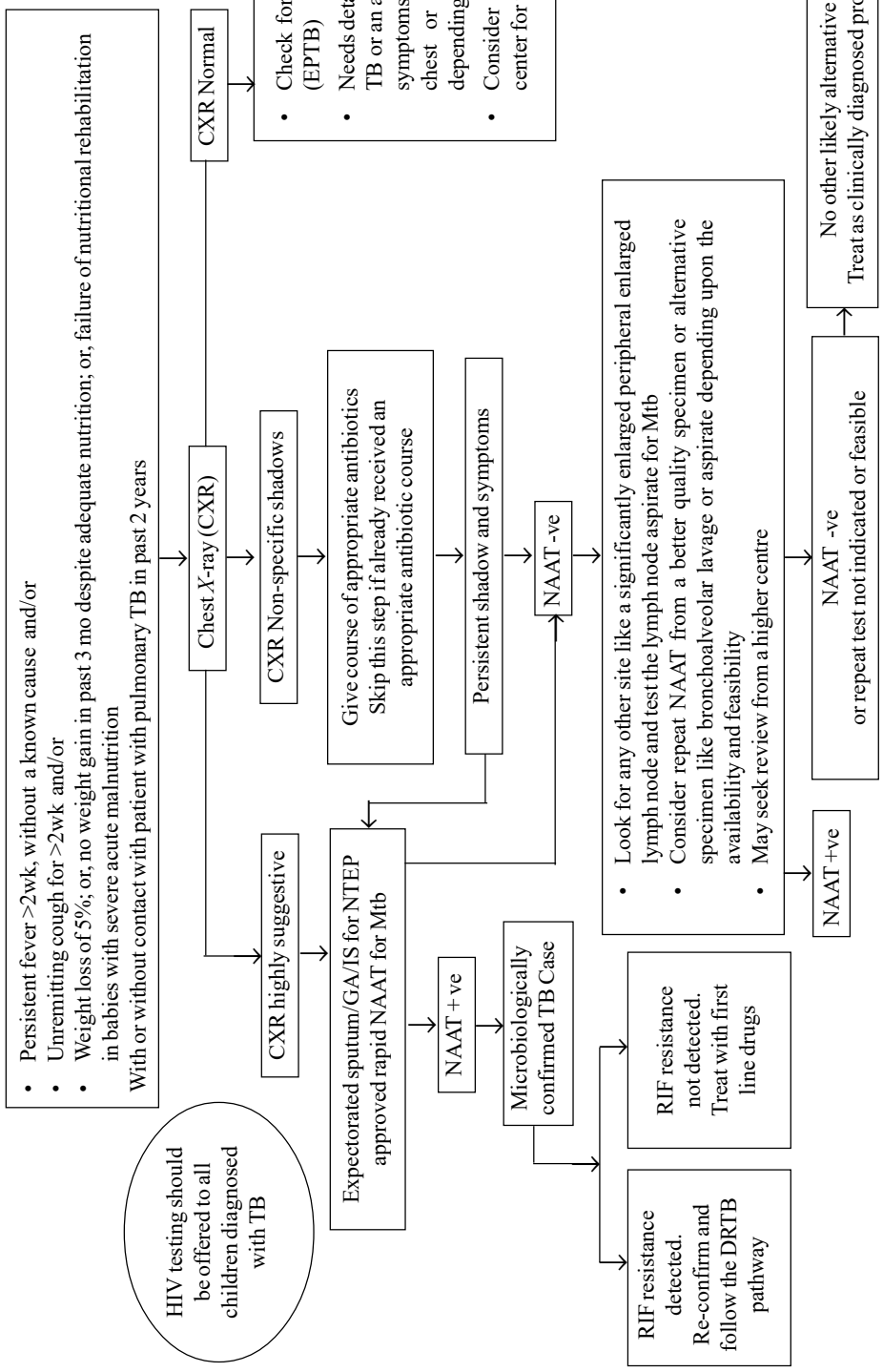
Conventional TB diagnostics for children involved appropriate use of clinical details, chest radiology and tuberculin skin test, with much less focus on microbiology, due to poor yield (AFB smear) or access issues (MTb cultures). U-DST strategy has led to change in the diagnostic pathways to include NAAT for every patient where a biological specimen can be procured. Routine chest imaging is done as initial screening test as testing of respiratory specimens from radiologically positive cases improves the yield of NAAT [4,5].

While NAAT has higher sensitivity than the smear, yet it fails in many paucibacillary cases. It is good only as a 'rule in' test and a negative NAAT does not rule out TB. The conventional methods of clinical diagnosis still need to be relied upon among those who are not confirmed by molecular tests. Current algorithm for evaluation of a child with pulmonary TB is shown in ***Fig.* 1**.

MANAGEMENT OF CHILDHOOD TB

What Is New in Treatment?

Treatment of TB has also evolved from erstwhile standard regimens based on the likely risk of drug resistance (new *versus* retreatment cases) to regimens based on identification of key resistance. The evidence available earlier in 70s suggested that the retreatment cases could be treated with a simpler 5 drug category II



Chest X-ray shall be done upfront in cases who are suspected to have TB but if a recent good quality chest X-ray is available, it need not be repeated. Highly suggestive chest X-ray refers to miliary shadows, or lymphadenopathy (hilar or mediastinal), or chronic fibro-cavitary parenchymal lesions; Non-specific chest X-ray: refer to patterns other than highly suggestive like consolidations, in-homogenous shadows or bronchopneumonia, etc.; NTEP approved NAAT shall be preferred over smear examination in all children. Available NTEP approved NAAT include Xpert Rif™, TrueNat™ and Line probe assay – If a specimen is positive by any of these methods, the case is labelled as microbiologically confirmed TB; At the initial step, if self-expectorated sputum is available and imaging /NTEP approved NAAT test is not available or delayed, smear may be done (for ease of availability and low cost); Whenever smear is used for diagnosis at least 2 samples should be tested while a single sample is sufficient for more sensitive NTEP approved NAAT; If a specimen is negative by NTEP approved NAAT (or smear), the second aliquot or a fresh good quality specimen should be submitted for a repeat NAAT and liquid culture; In case of Rif resistance is detected on NAAT, in a new case without any risk factors, a reconfirmation is desirable; Antibiotics of choice include amoxycillin or co-amoxyclav; Antibiotics like Linezolid or anyfluoroquinolone should not be used as they have anti-TB action; in case antibiotic trial has already been given in adequate dose and duration, it may not be repeated; Clinically-diagnosed probable TB case : Is a patient with a high clinical suspicion for TB disease based on suggestive symptoms, radiology and often supportive circumstances (history of exposure to a TB case) or evidence of infection (positive skin test for TB or positive IGRA) BUT the rapid microbiological tests are negative. Such a case may be treated as clinically diagnosed patient provided common alternative diagnoses have been ruled out. Where facilities exist, send one aliquot of the specimen for liquid culture, if the NAAT is negative for MTb.

DRTB: Drug resistant TB; GA: Gastric aspirate, NAAT-Rapid nucleic acid amplification test; NTEP: National tuberculosis elimination program.

Fig. 1 *Algorithm for pediatric intrathoracic tuberculosis (TB) among children with no risk factors for drug resistance.*

regimen. However, post implementation operational research and meta-analysis showed that this strategy was associated with increased risk of treatment failure with amplification of resistance to other companion drugs, particularly, if the patient was initially harboring rifampicin resistance [3,6]. With the feasibility of upfront rapid testing for rifampicin resistance, use of standard regimens without sensitivity testing is no more recommended for both the new as well as retreatment cases.

Likewise, the non-responders to initial regimen for drug sensitive TB (by 4 weeks) should be assessed again for presence of drug resistance (rifampicin and isoniazid at least). Non responsive cases with resistance to rifampicin and/or isoniazid are also tested for resistance to second line drugs like fluoroquinolones and the injectable aminoglycosides to provide the most suited regimens depending on the resistance pattern. The effort is to manage the cases as per the sensitivity to key drugs, thus improving outcomes and preventing further amplification of drug resistance. Retreatment cases with-out rifampicin resistance are now treated again with initial 4 drug regime while being tested for isoniazid resistance. In case of isoniazid (mono- or poly-) resistance, 6 month uniphasic 4 drug regime, where isoniazid is replaced by levofloxacin, is recommended. The IAP NTEP 2020 TB treatment guidelines are shown in ***Table* I** and **II**. The algorithm for evaluation of children with suspected drug resistance is shown in ***Fig.* 2**.

Table I Drug Regimen for Rifampicin-Sensitive Tuber-culosis as per IAP-NTEP Guidelines, 2020

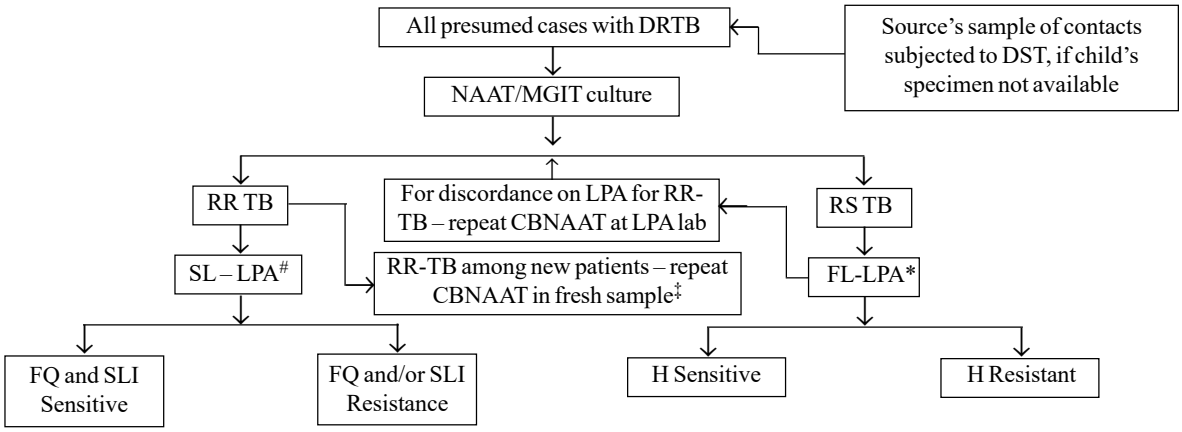
*Type of patient**	*Regimens*
New microbiologically confirmed pulmonary TB	2HRZE+
New clinically diagnosed pulmonary TB	4HRE[#]
New microbiologically confirmed extra-pulmonary TB	
New clinically diagnosed extra-pulmonary TB	
Previously treated TB ^(recurrence, treatment after loss to follow up, treatment after failure)	

*H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; *Molecular testing for rifampicin resistance shall be done in all new cases in children with suspected TB at diagnosis; #In case of neurological, bone, joints and spinal TB the continuation phase is extended to 10 months. In disseminated forms, the continuation phase might be extended to 7 months; ^All retreatment cases are to be evaluated as per DR-TB Algorithm. They were earlier treated with CAT II or retreatment regimen, which is now withdrawn. Their treatment should be based on drug sensitivity, particularly for R and I. In case they are found to be drug sensitive, they shall be started on the above regimen as for a new case.*

What Else Is New in Management?

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.

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



**First Line LPA (FL-LPA) may be done directly if smear positive; else, send for MGIT followed by FL-LPA to evaluate for R and H resistance; # Second Line LPA (SL-LPA) may be done directly if smear positive; else, send for MGIT followed by SL-LPA or Liquid culture DST (Mfx 2.0, Km, Cm, Lzd); ‡If Rifampicin Resistant on repeat test, DRTB regimen is initiated; If repeat test shows Rifampicin resistance not detected or If result is unavailable, DSTB regimen is initiated.*

Fig. 2 *Algorithm for evaluation of children with suspected drug resistant tuberculosis (DR TB).*

Table II Drug Regimen for Pediatric Drug-Resistant Tuberculosis as per IAP NTEP Guidelines, 2020

Type of tuberculosis	*Treatment regimen*	*Special considerations*
RR/MDR-TB without additional drug resistance to FQ and/or SLI* (Conventional Short Regimen – Initial regime for pulmonary TB & isolated pleural effusion or lymph node TB)	*Intensive phase* (4-6) Mfx^h Km Eto Cfz Z H^h E *Continuation phase* (5) Mfx^h Cfz Z E	• Recommended for pulmonary cases or non severe forms of EPTB like isolated lymph node disease or pleural effusion, etc. • Not exposed to reserve drugs • Send tests for SLI and FQ class resistance, continue this regimen only if sensitive to these two drug classes
MDR TB / MDR TB + FQ resistance / XDR – TB#, $, ‡ (All oral regime for children above 6 y)	*Intensive phase* 6-8 Dlm (Bdq) Lfx (Mfx^h) Lzd Cfz Cs *Continuation phase* 12 Lfx (Mfx^h) Lzd (l) Cfz Cs	• Not for severe EPTB like intracranial TB or disseminated TB • Not for children <6 y • Bdq to be replaced by Dlm in 6-17y age • Lfx to be replaced by Mfx^h if FQ class resistance
MDR TB(EP)/ Or MDR TB + FQ resistance/XDR - TB And Not eligible for all oral regime above	*Intensive phase* (6-9) Amika Mfx^h Lzd Cfz Eto Cs *Continuation phase* (18) Mfx^h Lzd (l) Cfz Cs	Disseminated or severe extra-pulmonary disease
Resistance to INH (with or without any non-rifampicin first line drug resistance) ^	*Uniphasic regime* (6) Lfx R E Z	Can be extended to 9-12 mo in extensive pulmonary disease and extrapulmonary disease like bone or intracranial

*RR: Rifampicin resistant; MDR: Multidrug resistant; XDR: Extensively drug resistant; EPTB: Extrapulmonary TB; FQ: Flouroquinolones; SLI: Second line injectables; Mfxh: High dose moxifloxacin; Km: Kanamycin; Eto: Ethionamide; Cfz: Clofazimine; Z: Pyrazinamide; Hh: High dose isoniazid; E: Ethambutol; Dlm: Delaminid; Bdq: Bedaquline; Lzd: Linezolid; Cs: Cycloserine; Lfx: Levofloxacin; *Shorter MDR TB regimen is of 9-11 mo with 4-6 mo of IP containing injectables and 5 months of CP. If the IP is prolonged, the injectable is only given three times a week in the extended intensive phase; #All oral longer MDR TB regimen is of 18-20 months; $New drugs like Bdq and Dlm would be given for 6 months duration while the dose of Lzd will be tapered to 10mg/kg/d (max 300 mg) after the initial 6-8 mo of treatment; ‡This regimen will also be used for treatment of XDR TB patients with 20 mo duration; ^All oral H mono/poly DR TB regimen is of 6 mo with no separate IP/CP.*

of isoniazid and high prevalence of malnutrition amongst the affected.

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) ≥40 kg would be managed as per the various weight bands described for adults.*

Current Status of Preventive Treatment

Goal to eliminate TB cannot be achieved timely unless the pool of cases with latent infection is treated. TB preventive treatment may now be extended to all household contacts of an infectious case after ruling out disease by symptom screening in line with WHO guidance. For children above 5 years, if facilities exist, one may test for presence of latent infection and then treat. But it is not mandatory to test for infection due to lack of simple and affordable point of care tests. TB preventive treatment is also recommended for any tuberculin skin test positive child who is receiving immunosuppressive therapy (children with nephrotic syndrome, acute leukemia, *etc.*), and a child born to mother who was diagnosed to have TB in pregnancy but has no evidence of disease [7].

Isoniazid is recommended for TB preventive treatment at a dose of 10 mg/kg/day for six months. No drugs are currently recommended for TB preventive therapy for the contacts of MDR TB cases but a close follow up for two years after exposure is recommended for timely

identification of those developing disease among exposed [8].

To conclude, the management of TB in children now has undergone a sea change with drug sensitivity directed therapy becoming the corner pillar. NTEP approved rapid NAAT has become the core investigative modality and erstwhile clinic-radiological approach of diagnosis is used only when NAAT fails in a clinically probable case. The pediatricians need also to be aware of the updated guidelines detailing change in regimens and drug dosages so that they can rationally manage TB among children.

Contributors: Both authors contributed to reviewing the literature, drafting, correcting and finalizing the manuscript.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. World Health Organization. The End TB Strategy. WHO; 2015.
2. Ministry of Health with Family Welfare. National Strategic Plan for Tuberculosis: 2017-25. Revised National Tuberculosis Control Programme. March 2017. Accessed September 16, 2020. Available from: *https://tbcindia.gov.in/WriteReadData/National%20Strategic %20Plan% 202017-25.pdf*
3. Central TB Division, Ministry of Health with Family Welfare. Technical and Operational Guidelines for TB Control in India 2016. Revised National Tuberculosis Control Program. MoHFW. Accessed September 16, 2020. Available from: *www.tbcindia.gov.in*
4. Raizada N, Sachdeva KS, Nair SA, *et al*. Enhancing TB case detection: Experience in offering upfront Xpert MTB/ RIF testing to pediatric presumptive TB and DR TB cases for early rapid diagnosis of drug sensitive and drug resistant TB. PLoS One. 2014;9:e105346.
5. Singh S, Singh A, Prajapati S, *et al*; Delhi Pediatric TB Study Group. Xpert MTB/RIF assay can be used on archived gastric aspirate and induced sputum samples for sensitive diagnosis of paediatric tuberculosis. BMC Microbiol. 2015;15:191.
6. Menzies D, Benedetti A, Paydar A, *et al*. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: A systematic review and meta-analysis. PLoS Med. 2009;6: e1000150.
7. Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management. World Health Organization; 2018.
8. Padmapriyadarsini C, Das M, Nagaraja SB, *et al*. Is chemoprophylaxis for child contacts of drug-resistant TB patients beneficial? A systematic review. Tuberc Res Treat. 2018: 3905890.