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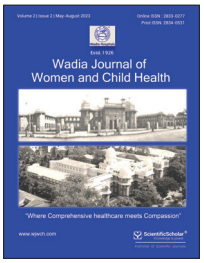

Invited Review

Newer perspectives - Diagnosis and management of pediatric tuberculosis

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ABSTRACT

Pediatric tuberculosis is a proxy indicator for the tuberculosis (TB) burden in the community. Although there has been a decline in the incidence, it is inadequate to meet the global goals for complete eradication of the disease. Childhood TB remains a challenge for clinicians and program managers. Advances in the diagnosis and treatment of pediatric tuberculosis are discussed in this review.

Keywords: Tuberculosis, Children, Recent advances, Treatment

INTRODUCTION

The global incidence of tuberculosis (TB) is 134 cases/100,000 population, with approximately 45% of the case burden in the South-East Asia region.[1] TB mortality accounted for 1.6 million deaths worldwide in 2021, which was higher in comparison than 2019 and 2020.[1] The number of drug-resistant TB (DR-TB) cases has also increased by 3.1%.[1] TB and human immunodeficiency virus (HIV), the development of DR-TB, and now the emergence of the TB-COVID pandemic are super-added problems. India ranks in the top eight countries that contribute to two-thirds of the global TB burden.[1,2] The incidence of TB in India is 188/100,000 population.[3] The total number of new and relapse cases in India as of December 2022 was 1,933,381, out of which, 6% were pediatric cases (0–14 years).[3] Only 54% of the total cases were bacteriologically confirmed.[4] In Mumbai itself, 65,617 cases were detected in 2022, and women made up for the larger proportion.[5]

Although there has been a decline in the incidence, it is inadequate to meet the global goals for complete eradication of the disease. For India, maximum surveillance efforts were executed under the National Tuberculosis Elimination Program (NTEP), with a total of 2.42 million cases and a notification rate of 172 cases/100,000 population which was an increase of 13% as compared to 2021.[4] Programmatically, TB in children has failed to gain enough momentum despite its high mortality and morbidity because the transmission rate from children is low due to the paucibacillary state. Pediatric TB is a proxy indicator for the TB burden in the community.[6]

Advances in the diagnosis and treatment of pediatric TB are discussed in this review.

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DIAGNOSIS OF TB

Early and accurate diagnosis of TB is the first strategy for improving the outcome of TB. Conventional diagnostic tools include microscopy and staining, culture on solid media, species identification using biochemical tests, and drug susceptibility on solid media. They are all time-consuming. Recently, there has been a shift from traditional practices to newer techniques which include fluorescent microscopy, liquid cultures, and molecular techniques.

SPECIMEN COLLECTION

The first step of diagnosis is adequate sample collection. The common samples selected for pediatric pulmonary tuberculosis (PTB) are gastric aspirate (GA) or gastric lavage (GL), sputum, stool and bronchoalveolar lavage, nasopharyngeal aspirate (NPA), and site-specific tissue samples such as cerebrospinal fluid (CSF), lymph node biopsy (LN), omental biopsy based on the clinical symptomatology.

According to the World Health Organization (WHO), stool is a newly recommended specimen for the diagnosis of pulmonary TB (PTB) in children using Xpert *Mycobacterium tuberculosis*/Rifampin (MTB/RIF) or Ultra. Children often swallow sputum containing TB bacilli and this passes through the digestive tract and is excreted in the stool. Hence, it is considered as a respiratory specimen. The required amount is 5 g or 1 teaspoon. It is easy to collect, feasible, and non-invasive. The stool has similar sensitivity and specificity compared to GA and sputum for the detection of TB.[7,8]

Table 1[9-12] describes the various samples and their details for the clinicians to decide on an appropriate sample for selection for further processing. It is important to note that the sensitivity of molecular tests for TB detection in pus, aspirate/biopsy specimen from LNs, other tissue samples, and CSF is low to moderately high but poor in pericardial, ascitic, and synovial fluid samples and still poorer in pleural fluid. A positive result by culture provides useful confirmation. However, a negative culture or nucleic acid amplification test (NAAT) cannot rule out TB due to the inadequate sensitivity of these tests in extrapulmonary specimens.

NEWER TECHNIQUES OF DIAGNOSIS

Liquid cultures

The following few liquid media are commonly used:

a) Mycobacterial growth indicator tube (MGIT) - MGIT system includes Middlebrook 7H9 broth with PANTA (polymyxin B, amphotericin B, nalidixic acid, trimethoprim, and azlocillin) antibiotic mixture to prevent the growth of contaminating organisms. It is a fluorescence-based technique and has a shorter turnaround time compared to solid LJ media. Rodrigues *et al*. tested over 14,000 specimens and observed that the mean detection time for MGIT was 9 days, and 38 days for LJ media in smear-positive specimens, and for smear-negative specimens the turnaround time was 16 days and 48 days for MGIT and LJ, respectively[13]
b) MB/BacT ALERT System - Similar to BacT ALERT blood culture system using Middlebrook 7H9 broth. It can be used to culture mycobacteria from any specimen other than blood
c) Versa TREK (Thermo Scientific) - This system consists of a cellulose sponge mimicking lung alveoli. It can also use blood as a specimen for the growth of bacilli with acceptable results[2]
d) BACTEC MYCO/F LYTIC – It is a blood culture system. It is designed to culture mycobacteria, fungi, and most aerobic bacteria. The bottle contains a lytic agent that helps to release mycobacteria from white blood cells (WBC).[2]

In a study by Crump *et al*., the performance of the BACTEC 13A (BD Diagnostic), BACTEC MYCO/F LYTIC (BD Diagnostic), BacT/ALERT MB (bioMérieux), and ISOLATOR 10 lysis-centrifugation (Wampole Laboratories) systems were evaluated. There was no significant change in yields between these systems. However, the mean detection time for MAC was shortest for BacT/ALERT MB, followed by BACTEC MYCO/F LYTIC, BACTEC 13A, and ISOLATOR 10.[14]

Immunodiagnosis

a. Interferon gamma (IFN-γ) release assay (IGRA) – IGRA can help differentiate infection between *M. tuberculosis* and other forms of mycobacteria as it assesses the T-cells response to two antigens produced by *M. tuberculosis* – culture filtrate protein 10 (CFP-10) and early secretory antigen target 6 (ESAT-6). Other forms of mycobacteria lack these antigens. The IFN-γ is then detected using enzyme-linked immunosorbent assay-based tests like QuantiFERON-TB Gold InTube (QFT-GIT, Cellestis, Australia) or QuantiFERON-TB Gold (QFT-G, Cellestis, Australia). Another IGRA that detects IFN–γ producing peripheral mononuclear cells after stimulation with CFP-10 and ESAT-6 is the enzyme-linked immunospot-based T-SPOT. QuantiFERON – TB GOLD PLUS is the latest generation method to identify the IGRA with the help of an additional antigen tube TB2. The TB1 tube contains ESAT-6- and CFP-10-derived peptides, designed to show cell-mediated immune responses from CD4+ helper T-lymphocytes. The TB2 tube contains new peptides able to elicit IFN-γ production by both CD4+ and CD8 + T-lymphocyte responses. CD8 + T-cells can improve performance in immunocompromised conditions that affect CD4+ T-cell responses (e.g., HIV)

Table 1: Sample collection for diagnosis of pediatric tuberculosis.

Sample	Quantity	Age	Procedure	Sensitivity (Xpert MTB RIF/Xpert ultra)	Specificity (Xpert MTB RIF/ultra)	Advantage	Disadvantage
Sputum	2–5 mL	>5 years	Expectoration of sputum early morning for 3 consecutive days	65–73%	97–99%	Low cost non-invasive	Not feasible in young children
Induced sputum	2–5 mL	Any age	Expectoration of sputum using MDI with salbutamol and 3% normal saline nebulization. Requires close monitoring of respiratory symptoms after the procedure.	65–73%	97–99%	Non-invasive	Requires multiple equipment and aerosol-producing procedures; hence, high risk to health care workers
Gastric aspirate	10–15 mL	<7 years	Nasogastric aspiration of gastric material containing swallowed sputum. Procedure to be done early morning after 4–6 h of fasting.	64–73%	95–98%	Feasible in young children	Requires trained personnel to invasive
Stool	5 g/1 teaspoon	Any age	Random stool sample uncontaminated by urine or toilet seat or bowl	53–61%	98%	Non-invasive	Requires additional laboratory processing
Bronchoalveolar lavage	3 mL	Any age	Bronchoscopy	81.60%	100%	Early detection of bacilli	Requires expertise, equipment, and trained personnel
Nasopharyngeal aspirate	2–5 mL	<7 years	Nasopharyngeal suctioning to collect secretions of the upper respiratory tract, or after cough stimulation	30–63.3%	98.2–99.9%	Non-invasive low cost	Requires equipment and trained personnel causes discomfort to the child
CSF	2 mL	Any age	Lumbar puncture	55.3–59.5%	100%	Low cost non-invasive	Requires expertise, sedation, and discomfort to the child
Serosal fluids	1–3 mL	Any age	Serosal fluid aspirate/biopsy	43.2–50.2%	98–99	Histopathology of the biopsy specimen can aid in diagnosis	Requires expertise, sedation, and discomfort to the child
Urine	2–5 mL	Any age	Clean catch-midstream urine sample	87%	91%	Detection of LAM has high sensitivity for children with HIV/severely immunocompromised	Poor sensitivity in immunocompetent children. Results may vary based on the method of collection
Fine needle aspiration biopsy	Based on type	Any age	Aspiration biopsy of different types of tissues (LN) based on clinical symptoms	84.4–90%	78.9%	Histopathology of the biopsy specimen can aid in diagnosis	Invasive requires expertise, equipment, and possible at a tertiary care center
Bone marrow	1–3 mL	Any age	Bone marrow aspirate	53–85.7%	97.3–100%	Useful in disseminated disease and in children with HIV	Requires expertise, equipment, and trained personnel

HIV: Human immunodeficiency virus, CSF: Cerebrospinal fluid, LN: Lymph node, MTB/RIF: *Mycobacterium tuberculosis*/Rifampin, LAM: Lipoarabinomannan, MDI: Metered dose inhaler

and improve discrimination of latent TB infection (TBI) from active TB.[15]

b. C-Tb (Statens Serum Institut, Copenhagen, Denmark) is the next-generation skin test for the detection of TBI, developed by SSI, Copenhagen. It is an easy-to-use point-of-care test. It can deliver IGRA-like performance in a skin test format and uses a universal 5 mm cutoff to differentiate the infected from the uninfected. The test is based on ESAT-6 and CFP-10 antigens (same as those used in IGRA) specific for *M. tuberculosis* and is unaffected by bacillus calmette guerin (BCG) vaccination.[8]

Molecular methods

NAAT was available from the mid-1990s for the diagnosis of TB.

Xpert MTB/RIF assay

The Xpert® MTB/RIF assay (Cepheid; Sunnyvale, CA, USA) amplifies nucleic acids through real-time polymerase chain reaction (PCR) using the Gene Xpert® platform. It integrates three processes (sample preparation, amplification, and detection) concerning *M. tuberculosis* deoxyribonucleic acid (DNA) and utilizes a technique that does not require the manipulation of mycobacterial DNA after amplification. *M. tuberculosis* and rifampicin resistance can be detected within 2 h.[2]

Xpert MTB-RIF Ultra

It was developed in 2017, for the identification of TB among the paucibacillary population. The limit of detection (LoD) of Xpert MTB/RIF assay is 131 colony-forming units (CFU)/mL and the LoD for Xpert Ultra is 16 CFU/mL. The WHO also recommends the use of Xpert Ultra as a first-line diagnostic test in children with signs and symptoms of PTB using sputum, GA, GL, NPA, and stool.[9]

Xpert MTB/extensively drug-resistant (XDR)® assay (Cepheid, USA)

It is a novel rapid, cartridge-based assay that is intended to be used as a follow-up test to any *M. tuberculosis* positive result for the detection of isoniazid (INH), ethionamide (ETO), fluoroquinolone (FQ), and second-line injectable resistance. Early studies of the Xpert MTB/XDR assay reported the LoD to be equivalent to Xpert MTB/RIF, with high estimated sensitivity (88.5–100%) and specificity (97.3–100%) for resistance detection in a clinical study of 310 clinical specimens. Studies have shown, it is a reliable assay for early identification of expanded resistance, but further studies are required in the pediatric population for widespread use.[16]

Truenat MTB and MTB Plus assays (Molbio Diagnostics, Goa)

They use chip-based real-time micro-PCR for the semiquantitative detection of *M. tuberculosis* complex directly from sputum specimens and can report results in less than an hour. The assays use automated battery-operated devices to extract, amplify, and detect specific genomic DNA loci. The assays are designed to be operated in peripheral laboratories with minimal infrastructure and minimally trained technicians. They are also recommended by the WHO for the detection of TB in children and adults with signs and symptoms of PTB, rather than culture and drug sensitivity testing (DST) testing as a first-line agent.[9]

TB-Loom mediated amplification test (TB-LAM)

The assay requires <1 h and is read under ultraviolet light with the naked eye. Loop primers speed up target DNA amplification to 10^9–10^{10} times within 15–30 mins. Amplified DNA is detected using SYBR green (DNA binding dye), magnesium pyrophosphate, or a non-inhibitory fluorescing agent. It is recommended for the detection of TB in adults (>15 years) with signs and symptoms of PTB.[17]

Line probe assay (LPA)

In LPA, target sequences are amplified using PCR primers. The amplified sequence is applied on substrates which lead to the formation of lines. The pattern formed is compared to a key for interpretation of results. LPA is approved by the WHO and is included in the national program of india for rapid detection of drug-resistant bacilli – first line and second line.[18] NTEP 2022 recommends the use of LPA to test for resistance to rifampicin, INH, and second like injectables, FQs. LPA has a lower sensitivity, hence the sample is subjected to LPA only if smear or Xpert positive. The disadvantage of LPA is the turnaround time which is 3–4 days.[8]

Whole genome sequencing

DNA sequencing of mycobacteria species, including Nocardia, has been used by various laboratories for research and diagnostic purposes.

Biomarkers

These are substances or components that serve as markers of disease activity, diagnosis of disease, or control of a therapeutic response. Commonly used biomarkers in children are erythrocyte sedimentation rate, and lipoarabinomannan (LAM). LAM is recommended by the WHO for diagnosis of TB in children with HIV/TB co-infection with signs of TB, or seriously ill, and in children with TB/HIV co-infection and CD4 <100/uL without signs of TB. It is a lateral flow

immunocapture assay to detect mycobacterial LAM antigen in the urine. It can be used as a bedside, point-of-care test but lacks sensitivity compared to molecular tests.[19,20]

MANAGEMENT OF TB

There has been a paradigm shift in the management of TB for children. Following are the key points adopted in the NTEP 2022 and WHO-Module 5. According to NTEP 2022, all presumptive TB cases are subjected to approve rapid molecular tests on appropriate specimens based on clinical symptoms to detect *M. tuberculosis* and Rifampicin resistance, which is used to identify multidrug-resistant TB (MDR-TB). This is possible using NAAT-based tests – Xpert MTB/Rif or Truenat and LPA for Xpert positive specimens or MTB isolates from cultures.[8] Hence, there is a programmatic shift to Universal DST for early identification of MDR TB. Patients are grouped as Drug-Sensitive (DS-TB) or DR-TB, based on upfront molecular tests on specimens selected according to clinical symptomatology.

Treatment of DS-TB

Treatment of DS-TB is biphasic, consisting of an induction phase (2 months) for rapid killing of bacilli and reducing infectivity and a continuation phase (CP) (4 months) for preventing relapses and failures. There is a usage of four drugs for DS-TB, consisting of INH, Rifampicin (R), Ethambutol (E), and Pyrazinamide (PZA). All four are used daily in the intensive phase and INH, R, and E are used daily in the CP. There is no extension of the intensive phase after 2 months. All medications are administered daily to reach a peak concentration.[8] In cases of neurological and spinal TB, the CP is extended for 10 months. Fixed drug combinations with pediatric formulations are available under NTEP. Adjunctive therapy with pyridoxine is recommended for all children.[8] A key recommendation by the WHO is shortening the therapy from 6 months to 4 months for non-severe TB for children aged 3 months–16 years. This is based on the results of the SHINE trial—a noninferiority, open-label trial, which randomized children below 16 years from 3 countries in Africa and India with symptomatic, non-severe, smear-negative, and DS-TB to 6-mo regime of 2HRZ(E) and 4HR(E) or 4-mo regime of 2HRZ(E) and 2HR(E). Treatment success was reported in 97.1% in the 4-mo regime versus 96.9% in the 6-mo regime.[21] This has not been adopted in the national program as yet.

Another recommendation is to switch to INH, R, PZA, and ETO for TB meningitis (TBM) (DS or radiologically confirmed) for 6 months. Although it has shown promising results in two trials in India and South Africa, it has not been adopted in the national program yet due to background resistance of INH being 12–14%. The results of the Phase 2 TBM Kids trial and short intensive treatment for children with tuberculous meningitis (SURE) trial are awaited to bring a change in drug regimen for DS-TBM.[9,22]

Treatment of DR-TB

Bedaquiline (BDQ) and Delamanid (DLM) are newer drugs now introduced for management of DR-TB. DLM is a nitroimidazooxazole compound whose mechanism of action is inhibition of the synthesis of mycolic acid which is a major component of the *Mycobacterium* cell wall. BDQ has a half-life of 5 and a half months and belongs to the diarylquinoline family of drugs, which specifically inhibits mycobacterial adenosine 5'-triphosphate synthase, which is essential for the generation of energy in MTB. Apart from gastrointestinal adverse effects, the toxic effect of most concern is their ability (BDQ > DLM) to cause QTc prolongation (QTc >450 ms or >60 msec from baseline). The WHO now recommends the use of BDQ and DLM for all children based on new but small pharmacokinetic studies that report drug exposure in the relevant age groups similar to that of adults with weight-based dosing and no significant cardiac adverse effects.[22,23] The consolidated guidelines on DR-TB as per the WHO now recommends a fully oral, shorter regimen lasting for 9–11 months, replacing the previously shorter regimen with an injectable agent. A shorter regimen is advised for non-severe MDR-TB. All other patients are prescribed a longer regimen.

Pretomanid is a new nitroimidazole recommended by the US food and drug administration as part of a regimen containing bedaquiline and linezolid for extensively drug resistant (XDR-TB) in adults. However, it is currently not recommended for children as the safety of the drug is yet to be evaluated. The centre for disease control (CDC) included the novel drug as part of their regimen in 2019. Programmatic introduction of the BPaL regimen (bedaquiline, pretomanid, and linezolid) with/without moxifloxacin was done in November 2021 as part of STOP TB. The dose of linezolid was 1200 mg, as compared to 600 mg. A field guide was released for the management of adults on BPaL regimen, and observation of toxicities.[24] Finally, in May 2022, the WHO recommended the use of this regimen worldwide. It is yet to be initiated in India.[9]

CONCLUSION

Diagnostic and management of TB have transitioned from programmatic execution to a more flexible approach to children, with the development of novel drugs and strategies as evidence emerges. Although it may not be possible to implement some of the newer guidelines in India, they are sure to shape the future and provide a different perspective to the practicing clinicians.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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