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Special Issue on Pediatric Tuberclosis

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President's Message

Dear colleagues and friends

It's a great moment for all of us to meet and interact at the RESPICON 2022, Annual conference of Pediatric Respiratory Society Delhi and NCR organized at Sir Ganga Ram Hospital, New Delhi on 20th November 2022. On this great occasion, we are coming up with second issue of Pediatric Respirology Journal. This is in fact a special issue dedicated to Pediatric Tuberculosis. We were fortunate to have Prof (Dr) Varinder Singh, Director, Pediatric Pulmonology & Professor Pediatrics, Kalawati Saran Children Hospital & Lady Hardinge Medical College, New Delhi as guest editor. Prof Varinder Singh is a well know academician and teacher of pediatrics and pediatric Pulmonology. He is an authority on pediatric tuberculosis. I am so happy and sincerely thankful to him for accepting my invitation to edit the current issue inspite of his busy schedule.

Tuberculosis is a vast subject and many changes in the diagnosis and treatment have been implemented in the National Tuberculosis Elimination Program. Newer diagnostic tests, drugs and drug regimens have been introduced. Similar changes have occurred in pediatric tuberculosis. I thought it is the right time to bring out a special issue on pediatric tuberculosis. I am extremely thankful to all the authors for their contributions. We will be publishing more of disease specific issue of Pediatric Respirology Journal in future. I will be very happy to have your inputs on this.

I wish all the delegates a very interactive and learning experience at RESPICON 2022.

Regards

Dr Anil Sachdev
Editor-in-Chief
President
Pediatric Respiratory Society Delhi & NCR

Recent Updates on Diagnostic Tests for Pediatric Tuberculosis

Prof (Dr) Kamal K Singhal. DCH, MD, DM
Division of Pediatric Pulmonology, Department of Pediatrics,
Lady Hardinge Medical College and Kalawati Saran Children Hospital, New Delhi 110001

Abstract

Of all the deaths attributed to infectious causes, tuberculosis is responsible for the most number of deaths resulting from a single infectious agent. Tuberculosis is a global public health problem, a crisis further compounded by the emergence of drug resistant strains. Expeditious and effective treatment helps prevents the development of drug resistant strains. Thus, it is imperative to have fast and reliable point-of-care (POC) diagnostic methods to diagnose both tubercular disease and drug resistance, thereby facilitating effective and early treatment. Here, we review the currently in clinical use, as well as the promising newer methods currently in the realms of research such as Whole genome sequencing (WGS) and Newer generation sequencing (NGS).

Keywords: Tuberculosis, diagnostics, MGIT, Lowenstein Jensen, Tuberculin skin test, Quantiferon-TB gold, PCR, LAMP, VOC, whole genome sequencing, next generation sequencing.

Introduction

Tuberculosis is an infectious disease spread primarily via the airborne route. It is caused by *Mycobacterial tuberculosis* (MTB) and primarily affects the pulmonary system, which constitutes around 80 % of the total cases of tuberculosis. Other than the pulmonary system it also affects the intestine, meninges, lymph node, bone, joint, kidney and skin which are referred to as extrapulmonary tuberculosis (EPTB). The two factors which determine whether the pathogen will be eliminated or will continue to persist in the body are: the host's immune status and the bacillary load. Clinically, the disease spectrum of tuberculosis extends from an asymptomatic and non-transmissible state termed latent TB, to the symptomatic and transmissible disease state.(1) Although tuberculosis is a major public health problem globally, low and middle-income countries are more severely affected. The synergistic association of tuberculosis with Human Immunodeficiency Virus (HIV) and the emergence of multidrug

resistant (MDR) and extensively drug resistant (XDR) tuberculosis strains have further exacerbated the situation.(2)

The diagnosis of tuberculosis especially in children remains challenging and the factors contributing to this include: paucibacillary TB disease in young children, lack of sensitive point-of-care diagnostic tests, lack of suitable respiratory samples and misdiagnosis due to the overlapping of non-specific TB symptoms with other common childhood illnesses.

Clinical diagnostic approach

Clinical presentation of tuberculosis is very variable and only 5 to 10% of the affected individuals have clinical signs and symptoms. It primarily affects the pulmonary system and the presentation may include chronic productive cough, hemoptysis, low-grade fever, night sweats, loss of appetite, malaise, fatigue, and weight loss.(3) There may be an active pulmonary tuberculosis contact. The clinical presentation in extrapulmonary TB can be variable and the manifestations are dependent on the system primarily involved.

Integrated treatment-decision algorithm: Recently WHO, in a conditional recommendation, has suggested using an integrated person-centred care model to diagnose pulmonary TB, in children with presumptive pulmonary TB.(4) This is meant to minimize, the barriers and delays resulting from TB infection testing and the losses associated with tubercular infection care cascade. "Integrated" means evaluating for TB infection and disease in parallel, whereas "person-centered care" means coordinating multiple care-activities during the same visit. This model is likely to shorten delays to appropriate treatment initiation and reduced cost burden while promoting retention in the TB infection cascade of care. An extension of "patient-centered care" is "family-centered care" wherein the care of the entire family is coordinated to minimize the time and cost burden on the family. Useful for contact investigation in the household, this approach is more cost effective and results in higher yield and retention in treatment. Thus during the first encounter with healthcare facility, screening for TB disease should be combined with the testing for TB infection. If symptoms are suggestive of TB disease, further evaluation should be done as soon as possible, preferably on the same visit. The second visit, 48 to 72 hours later, should be optimized for assessing the tuberculin skin test (TST) or Interferon-gamma release assay (IGRA) result; evaluating the results of the submitted microbiological tests for TB;

doing a clinical evaluation to rule out TB or before starting TB treatment; depending on the clinical and investigative profile starting either tuberculosis preventive treatment (TPT) or TB treatment.

In children younger than 15 years of age, having close contact with someone with tuberculosis, systemic screening for tubercular disease may include the use of a symptom based screen (either cough, fever, poor weight gain); or chest X ray; or both.(4) In children younger than 10 years living with HIV, systemic screening should include symptom screen (cough, fever, poor weight gain or close contact with TB patient). In children aged 15 years and older, requiring screening for tuberculosis, WHO in a conditional recommendation suggests systemic screening utilizing a symptoms based screen, chest radiograph or molecular rapid diagnostic test (WHO recommended), either alone or in combination.(4)

Clinical score:

Clinical scores have been used as case-finding tools for tuberculosis among patients infected with HIV. A cross-sectional feasibility study was conducted by Aunsborg JW et.al. to assess the practicality of implementing the TB score in the routine clinical settings, for newly diagnosed HIV infected patients. They evaluated a clinical cohort of previously HIV infected patients, aged 15 years or more, not started on tuberculosis within the past one year. The symptoms asked for included, self-reported cough, dyspnoea, night sweats, hemoptysis, and chest pain; while the signs included were anemia, tachycardia, positive finding on lung auscultation, fever, low body mass index (BMI), and lower mid-upper arm circumference (MUAC). One point was assigned for each symptom and sign, with a maximum possible score of 13. The final diagnosis of tuberculosis was based either on sputum positive for Xpert or the presence of acid fast bacilli (AFB) on smear microscopy or clinical judgment or radiological persistent pneumonia despite the short course of antibiotics. The cut-off value of 2 from the score had a high sensitivity and NPV of 95.5% and 97.6% respectively but low specificity and positive predictive value of 36.9% and 23.1% respectively. Thus, scanty data suggests that the TB scores provide a systemic approach to identify newly diagnosed HIV patients at high risk of TB, in whom additional investigations can be prioritized.(5)

Radiography

Chest radiography is a useful screening tool. It may help differentiate primary from secondary disease. The primary disease involves a single lung parenchyma lesion in the right middle lobe or lower lobe (Ghone's focus) with an enlarged draining lymph node. This combination of Ghone's focus and the enlarged lymph node is known as the Ghone's complex. In tuberculosis compared to other bacterial infections the size of the draining lymph node is larger commensurate to the parenchymal lesion. The endogenous reactivation, on the other hand, more commonly seen in adolescents, on chest radiography has a predilection for the apical region with relatively unremarkable lymph nodes. The pattern on chest radiography highly suggestive of tuberculosis includes hilar lymph node, chronic fibrocavitary lesion, and military lesions. Although considered highly suggestive of tuberculosis in high endemic countries like India, the presence of these lesions does not indicate a definitive diagnosis of tuberculosis, which remains microbiology. Moreover, chest radiological lesions do not help diagnose latent tuberculosis infection. In a conditional recommendation, WHO suggests use of computer aided detection software programme in place of human readers, for interpreting digital chest radiographs, for screening and triage of tuberculosis disease.(4)

Microscopy for mycobacterium tuberculosis

Sputum is an important specimen for the diagnosis of pulmonary tuberculosis. In younger children unable to expectorate, induced sputum or gastric lavage specimen is useful. Acid-fast staining using Ziehl Neelsen stain on smear microscopy has been widely used for the diagnosis of tuberculosis. Limitation of this method includes its inability to differentiate Mycobacterium tuberculosis (MTB) from other acid fast bacilli such as Nontuberculous mycobacterium (NTM); low sensitivity. High bacilliary content in the specimen (5000-10000 CFU/ml) is required for smear microscopy to be positive. Fluorescence microscopy using auramine and rhodamine stain has relatively higher sensitivity in detecting acid fast bacilli. Overall, microscopy is a rapid, low cost and easy method with relatively low sensitivity and specificity.

Culture of Mycobacterium tuberculosis

Growth of M. tuberculosis on culture from a specimen is the gold standard to diagnose tuberculosis. Culture is a highly sensitive diagnostic method and can detect 10 to 100 viable bacilli in the cultured specimen material. In addition to high sensitivity, the culture of the

specimen to diagnose tuberculosis has high specificity (greater than 99%). Mycobacterium is usually cultured on Lowenstein Jensen (LJ) medium. On this solid medium, Mycobacterium tuberculosis form dry, rough, raised, irregular colonies with a wrinkled surface. The identification of MTB from the positive cultures till recently was dependent on biochemical tests for aryl sulphatase, Niacin, catalase-peroxide, neutral red nitrate reductase and amidase after incubation of 2 to 3 weeks. Cultures of mycobacterium can also be identified using DNA probes and reverse phase high-performance liquid chromatography (HPLC).(6) More rapid culture methods include the radiometric BACTEC method, Septic Check AFB and microcolony detection on solid media.

MGIT (BACTEC 960 system) and phenotypic drug-susceptibility testing

World health organization (WHO) in 2007 endorsed liquid culture system for identification and drug susceptibility testing of tuberculosis. MGIT BACTEC 960 has been the system of choice as it is non-radiometric, fully automated with a continuous monitoring system, and more user-friendly.(7) Compared to conventional L-J culture, MGIT960 is as effective in detecting the mycobacteria and its drug sensitivity pattern with markedly improved turnaround time.(8) Although useful in the initial detection of mycobacteria, additional tests are required for species identification.

Immunological test

Immunological tests include the Tuberculin skin test (TST) and Quantiferon-TB gold (QFT) and are primarily utilized as a screening tool.

TB infection skin test using M. tuberculosis specific antigens

Tuberculin skin test: TST is also known as the purified protein derivative test (PPD) or Mantoux test. Developed almost a century ago it is still being utilized as an initial screening tool for tuberculosis in industrialized countries. It requires an intra-dermal injection of purified protein derivative and the result is read 48 to 72 hours later. It requires well-trained personnel for injection and interpreting the result and the patient needs to visit the health facility twice. It is of utility in detecting exposure to mycobacterium in countries with a low prevalence of tuberculosis. High prevalence of mycobacterium infection, BCG vaccination and non-

mycobacterial infection can result in false positivity. The sensitivity of this test is low in immunocompromised individuals. The original so-called "old tuberculin" was replaced by a standard preparation of PPD from M. tuberculosis in 1941. A single standard lot was produced by Florence Seibert and termed "PPDS". Since then many new tuberculin materials have been produced using the same methodology and have been standardized against this PPDS.

Cy-Tb: It was previously called the C-Tb test (Serum Institute of India) and contains two recombinant proteins of ESAT-6 and CFP-10 in a ratio of 1:1. It is to be administered using the Mantoux method and also read 48-72 hours later. No severe adverse reaction has been reported with Cy-Tb.

Diaskin test: Produced by Generium, Russian Federation, it is a recombinant protein produced by a genetically modified culture of E.coli BL21/pCFP-ESAT. It is also to be administered intradermally and read 48 to 72 hours later. The manufacturer indicated that in 55,774,995 tests, done between the years 2019 and 2021, a total of 27 serious and 30 non-severe adverse effects were reported but further details are not available. It is contraindicated in acute and chronic infections (except for presumptive TB); somatic and other diseases during exacerbation; epilepsy; allergic conditions; common skin diseases; and hypersensitivity to the active substance or to any of the excipients in the product.

C-TST: Previously known as the ESAT6-CFP10 test (Anhui Zhifei Longcom, China), it is a ESAT-6-CFP-10 fusion recombinant protein expressed in genetically modified E.coli. It is to be given intradermally and read 48 to 72 hours later. Data from phase 3 trial are awaited.

Quantiferon TB gold

It is an interferon-gamma release assay to measure cell-mediated immune response. Commonly used as an alternative to TST. The test involved the collection of a blood sample using MTB antigen coated tubes and the interferon gamma release is measured using Enzyme immunoassay technique. Unlike TST, for this test, the patient needs to visit the health facility and the result is not affected by BCG vaccination or non-tubercular mycobacterium (NTM) infection. Compared to TST, Quatiferon TB gold test is more costly. Similar to TST, it cannot differentiate MTB infection from disease. WHO, strongly recommends use of either TST or IGRA to test for TB infection.(4)

Molecular diagnostic tests

Molecular diagnostic tests have utility both for the diagnosis of MTB infection and for the detection of drug resistance. Moreover, its results are rapidly available thereby helping in the clinical management of patients. The various molecular methods used are polymerase chain reactions (PCR), strand displacement amplification (SDA), transcription mediated amplification (TMA), Q-beta replicase amplification, oligonucleotide ligation, reporter mycobacteriophage system and amplification. The PCR-based tests have been further developed over the last decade for diagnosis and molecular characterization of mycobacterium by targeting the various genes of MTB. PCR is a valuable and cost effective technique for quick mycobacterial detection in different clinical specimens. (9)

Loop mediated isothermal amplification (LAMP)

WHO has endorsed loop mediated isothermal amplification (LAMP) method for the diagnosis of active tubercular disease in laboratories set up in peripheries. It is a cost-effective, simple, specific nucleic acid amplification method. It utilizes a different set of primers specifically designed to recognize the target genes and gives rapid results. The operational feasibility of this method has been evaluated for the diagnosis of MTB in highly endemic countries and has been successfully implemented.(10) The overall sensitivity and specificity of this assay has been in the range of 76-80% and 97-98% respectively.(11)

Line probe assay (LPA)

LPA is useful in detecting the presence of MTB as well as mutations determining drug resistance through the amplification using PCR and subsequent hybridization on a strip immobilized with specific oligonucleotide probes. WHO has endorsed the use of LPA as an initial test, only in a smear-positive sputum specimen (due to its relatively lower sensitivity) or a cultured isolate of Mycobacterium tuberculosis complex (MTBC), for the detection of resistance against the first-line antitubercular agents (isoniazid and rifampicin). Similarly second line LPA has been recommended to detect resistance to second line anti-mycobacterial drugs (fluoroquinolones and second line injectable drugs).(12)

Xpert MTB®/RIF

XpertMTB®/RIF is a cartridge-based nucleic acid amplification technique and utilizes real-time multiplex PCR for a region of *rpo* B gene specific to MTB. Rifampicin resistance determining mutation is further detected by molecular beacon technology.(13) Also referred to as "laboratory in cartridge" it is a robust, simple-to-operate test with a lower biohazard risk and a rapid turnaround time of around 90 minutes.(14) The sensitivity of this test is 98% and 70% for smear positive and smear negative samples respectively.(15,16) The sensitivity and specificity of this test on culture positive specimens are 85% and 98% respectively.(17) By detecting rifampicin resistance it predicts the presence of Multidrug resistant TB (MDRTB) (resistance to both rifampicin and isoniazid), as epidemiologically isoniazid resistance is more prevalent than rifampicin resistance. Recent evidence suggests that in settings with a low burden of MDR more than 40% of rifampicin resistant isolates were susceptible to isoniazid.(18) Also as per one report around 27% of rifampicin susceptible cases were resistant to at least one first line drug.(19) Thus, even though it offers a distinct advantage in clinical practice due to its rapid turnaround time, the gold standard remains the culture whose sensitivity and specificity are still better than any other test.

Xpert Ultra: Given the low sensitivity of XpertMTB®/RIF in smear-negative TB and children living with HIV; (Xpert Ultra) was developed as the next-generation assay by Cepheid, Sunnyvale, United States. It uses the same GeneXpert platform as XpertMTB®/RIF and has a lower detection limit with an additional "trace" semi-quantitative category. Recent WHO guidelines, strongly recommend Xpert Ultra as the initial diagnostic test for tuberculosis and detection of Rifampicin resistance on sputum, nasopharyngeal aspirate, gastric aspirate (GA) or stool, instead of smear microscopy or culture and phenotypic drug susceptibility testing (DST), in children with signs and symptoms suggestive of pulmonary tuberculosis.(4) There is paucity of data on the use of XpertUltra in children with severe acute malnutrition (SAM) and children living with HIV but the WHO expert panel concluded that Xpert Ultra on GA, stool, nasopharyngeal aspirate and sputum samples can be used in children in these subgroups as well, as the preferred initial diagnostic test for pulmonary TB. The stool needs to be processed using centrifuge-free stool-processing methods before using Xpert Ultra. Although, found to be easy to process by the laboratory personnel in reference laboratories these methods cannot be performed

by non-laboratory personnel such as nurses or health care workers in primary health centers (PHC) settings without access to a laboratory. In children, given the paucibacillary nature of the disease, the "trace" results are common with the use of Xpert Ultra. Thus for children and people living with HIV, being evaluated for pulmonary TB, "M. tuberculosis complex detected trace" result is considered a "bacteriological confirmation" of TB. The samples with "trace" results with have an indeterminate result for detecting Rifampicin resistance. This necessitates collecting an alternative sample for Xpert Ultra processing if the likely hood of drug resistant disease is high.

WHO strongly recommends that in children with signs and symptoms of Tubercular meningitis (TBM), Xpert MTB/RIF or Xpert Ultra should be the initial diagnostic test for cerebrospinal fluid (CSF) evaluation rather than smear microscopy or culture.(4) WHO conditional recommendation suggests that in children with signs and symptoms suggestive of extrapulmonary TB, Xpert MTB/RIF may be used as the initial diagnostic test to evaluate lymph node aspirate or biopsy, pericardial fluid, pleural fluid, peritoneal or synovial fluid or urine specimens rather than smear microscopy/culture.(4) It strongly recommends Xpert MTB/RIF or Xpert Ultra for rifampicin-resistance detection rather than culture and phenotypic DST.(4)

Truenat®MTB: This assay developed by Molbio Diagnostics, India has been endorsed by WHO for rapid detection of TB (Truenat MTB and Truenat MTB Plus) as well as rifampicin resistant MTB (Truenat MTB-Rif Dx). It has high sensitivity and specificity of 83 and 98% respectively. The accuracy of Truenat®MTB-Rif Dx assay to detect sequentially detect rifampicin resistance is comparable to Xpert MTB/RIF, Xpert Ultra and LPA.(20) In a conditional recommendation, in children with signs and symptoms of pulmonary TB, WHO recommends Truenat MTB or MTB Plus as the initial diagnostic test for, but Truenat MTB-RIF Dx as an initial test for rifampicin resistance (rather than culture and phenotypic DST).(4)

Current evidence supports the use of: low complexity automated NAATs (Xpert MTB/XDR (Cepheid)) for the detection of resistance to isoniazid and second-line anti-TB agents (fluoroquinolones, ethionamide, amikacin); moderate complexity automated NAATs (Abbott RealTime MTB and Abbott RealTime MTB RIF/INH (Abbott), FluoroType MTBDR and

FluoroType MTB (Hain Lifescience), BD MAX MDR-TB (Becton-Dickinson), cobas MTB and cobas MTB-RIF/INH (Roche)) for the detection of TB and resistance to rifampicin and isoniazid; and high complexity hybridization-based NAATs (Genoscholar PZA-TB II (Nipro)) for the detection of resistance to pyrazinamide.

Future of Tuberculosis diagnostics

Face mask sampling: In a recent study, Caroline MW and colleagues assessed the efficacy of face mask sampling as a diagnostic test modality for TB. They did a 24-hour long longitudinal study in three hospitals in South Africa wherein patients underwent one hour of face mask sampling eight times in a 24 hour period with simultaneous sputum sampling. MTB was detected using quantitative PCR. A total of 24 patients who completed the study majority (20) had HIV co-infection. MTB was detected in 166 (86%) of the 192 face-mask samples and 38(21%) of the 184 sputum samples over 24 hour period. The study suggested that face mask sampling offers a highly efficient and non-invasive method for detection of exhaled MTB and had higher consistency compared to sputum samples. It has potential for diagnosis and screening especially in difficult-to-reach communities.

Newer genetic testing such as **whole genome sequencing (WGS)**, allows highly precise sequence read of the entire genome of a microorganism.(21) It is a **next generation sequencing (NGS)** based technology and has been used successfully for the characterization of the organism, genotyping, epidemiological investigations and drug susceptibility testing of tuberculosis. Compared to XpertMTB/RIF and line probe assay which identify only a limited number of mutations, WGS can detect and functionally characterize all the mutations. It can also identify the resistance determining mutations in newer drugs like delaminid and bedaquilline. With the availability of open source, user friendly databases for identification of genomic data the WGS may evolve from a research tool to clinically useful technique.

Volatile Organic compound test (VOC) is a new technique which has future diagnostic potential. Still, in the realms of research laboratory, it may be useful as a noninvasive inexpensive test for use in pediatric and critically sick patients once it is clinically available.

One such device, “eNose” has been developed and used in patients in Paraguay with a sensitivity and specificity of 88% and 92% respectively.(22)

Lateral flow urine lipoarabinomannan assay (LF-LAM): LAM is used to detect mycobacterial lipoarabinomannan antigen in urine collected non-invasively. It is emerging as a potential point-of-care test for the diagnosis of tuberculosis. The test currently available has suboptimal sensitivity, not appropriate for use in all populations. It has better sensitivity when used in HIV positive patients. WHO has recently updated its policy on the usage of LAM, in the diagnosis of active tuberculosis, in patients with HIV infection. There is a strong recommendation from WHO to use LAM in the diagnosis of active tuberculosis in adults, adolescents and children living with HIV with signs and symptoms of pulmonary or extrapulmonary tuberculosis; advanced HIV disease or those who are serious illness; CD4 cell count less than 200 cells/mm3 (inpatient setting) or less than 100/mm3 (in outpatient setting) independent of the clinical signs and symptoms. LF-LAM is not recommended in the outpatient settings in adults, adolescents and children living with HIV in whom clinical evaluation for symptoms of tuberculosis has not been done or CD4 cell count evaluation has not been done or it is more than 200. All patients with clinical manifestations of pulmonary tuberculosis and producing sputum, before LF-LAM, should have at least one sputum evaluation with Xpert®MTB/RIF assay.(23) Although still in still in early stages of development VOC and LF-LAM are promising propositions.

Conclusion:

Radiological investigations can suggest but are not pathognomic for the diagnosis of tuberculosis. Although the conventional bacteriological and immunological tests are capable of both screening as well as diagnosis of TB, the Nucleic acid amplification tests (NAATs) have provided a rapid and reliable point-of-care test, useful even in peripheral laboratories. WHO-endorsed NAATs are highly sensitive and specific tests with very rapid turnaround-time, and detect M. tuberculosis from all types of clinical specimens including sputum, in addition to detecting resistance to Rifampicin. The availability of well-defined clinical criteria to define presumptive tuberculosis and an integrated person-centered care model can also facilitate the diagnosis of tuberculosis with judicious utilization of resources. Currently, there is a need,

especially in children, to develop improved techniques to collect more representative and less invasive specimens. The future of TB diagnostics remains on the application of WHO-endorsed NAATs in the peripheral laboratories and bringing genetic tests such as whole genome sequencing (WGS) and next generation sequencing (NGS) from the realms of research laboratory to the clinical settings.

Reference:

1. Barry CE, Boshoff HI, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol. 2009 Dec;7: 845–855.

2. Sanchez-Padilla E, Merker M, Beckert P, et al. Detection of drug-resistant tuberculosis by Xpert MTB/RIF in Swaziland. N Engl J Med. 2015 Mar 19;372: 1181–1182.

3. Acharya B, Acharya A, Gautam S, et al. Advances in diagnosis of Tuberculosis: an update into molecular diagnosis of Mycobacterium tuberculosis. Mol Biol Rep. 2020 May;47: 4065–4075.

4. WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents - PAHO/WHO | Pan American Health Organization [Internet]. [cited 2022 Oct 16]. Available from: https://www.paho.org/en/documents/who-consolidated-guidelines-tuberculosis-module-5-management-tuberculosis-children-and

5. Aunsborg JW, Hønge BL, Jespersen S, et al. A clinical score has utility in tuberculosis case-finding among patients with HIV: A feasibility study from Bissau. Int J Infect Dis. 2020 Mar;92S:S78–884.

6. Sepkowitz KA, Raffalli J, Riley L, et al. Tuberculosis in the AIDS era. Clin Microbiol Rev. 1995; 8: 180–199.

7. Cruciani M, Scarparo C, Malena M, et al.. Meta-analysis of BACTEC MGIT 960 and BACTEC 460 TB, with or without solid media, for detection of mycobacteria. J Clin Microbiol. 2004 May;42:2321–2325.

8. Giampaglia CMS, Martins MC, Vieira GB de O, et al. Multicentre evaluation of an automated BACTEC 960 system for susceptibility testing of Mycobacterium tuberculosis. Int J Tuberc Lung Dis. 2007 Sep;11: 986–991.

9. Gholoobi A, Masoudi-Kazemabad A, Meshkat M,et al. Comparison of Culture and PCR Methods for Diagnosis of Mycobacterium tuberculosis in Different Clinical Specimens. Jundishapur J Microbiol. 2014; 7: e8939.

10. Pandey BD, Poudel A, Yoda T, et al. Development of an in-house loop-mediated isothermal amplification (LAMP) assay for detection of Mycobacterium tuberculosis and evaluation in sputum samples of Nepalese patients. J Med Microbiol. 2008; 57: 439–443.

11. World Health Organization. The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis: policy guidance [Internet]. World Health Organization; 2016 [cited 2022 Oct 5]. Available from: https://apps.who.int/iris/handle/10665/249154

12. World Health Organization. The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance [Internet]. World Health Organization; 2016 [cited 2022 Oct 5]. 42 p. Available from: https://apps.who.int/iris/handle/10665/246131

13. Lawn SD, Nicol MP. Xpert® MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. Future Microbiol. 2011; 6: 1067–1082.

14. Pinto LM, Udwadia ZF. Xpert MTB/RIF and pulmonary tuberculosis: time to delve deeper? Thorax. 2013; 68: 987–988.

15. Helb D, Jones M, Story E, et al. Rapid detection of Mycobacterium tuberculosis and rifampin resistance by use of on-demand, near-patient technology. J Clin Microbiol. 2010 ; 48: 229–237.

16. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med. 2010; 363: 1005–1015.

17. Li S, Liu B, Peng M, et al. Diagnostic accuracy of Xpert MTB/RIF for tuberculosis detection in different regions with different endemic burden: A systematic review and meta-analysis. PLoS One. 2017;12(7): e0180725.

18. Smith SE, Kurbatova EV, Cavanaugh JS, et al. Global isoniazid resistance patterns in rifampin-resistant and rifampin-susceptible tuberculosis. Int J Tuberc Lung Dis. 2012 ; 16: 203–205.

19. Fasih N, Rafiq Y, Jabeen K, et al. High isoniazid resistance rates in rifampicin susceptible Mycobacterium tuberculosis pulmonary isolates from Pakistan. PLoS One. 2012;7: e50551.

20. World Health Organization. Molecular assays intended as initial tests for the diagnosis of pulmonary and extrapulmonary TB and rifampicin resistance in adults and children: rapid communication [Internet]. World Health Organization; 2020 [cited 2022 Sep 21]. 8 p. Available from: https://apps.who.int/iris/handle/10665/330395

21. Schwarze K, Buchanan J, Taylor JC, et al. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. Genet Med. 2018 ; 20: 1122–1230.

22. Coronel Teixeira R, Rodríguez M, Jiménez de Romero N, et al. The potential of a portable, point-of-care electronic nose to diagnose tuberculosis. J Infect. 2017; 75:441–447.

23. Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV, 2019 Update [Internet]. [cited 2022 Oct 14]. Available from: https://www.who.int/publications-detail-redirect/9789241550604

Regimens for Treatment of Tuberculosis in Children

Dr Ritika Goyal, MD, DNB
European Diploma Pediatric Respiratory Medicine
Consultant Pediatric Pulmonology
Sitaram Bhartia Institute of Science and Research
Max Hospital Shalimar Bagh
New Delhi

Introduction:

Treatment regimens for tuberculosis (TB)in children and adolescent has undergone many modifications with the availability of new drugs and based on new research over the last decade. New drugs like bedaquilline and delaminid that are now approved for pediatric age group have been incorporated in recent regimens for treatment of multidrug resistant/Rifampicin resistant tuberculosis (MDR/RR TB) described by WHO[1]. Based on the SHINE study done to evaluate the shorter regimen for treatment of drug sensitive TB (DS-TB) in children less than 6 years of age, WHO has now recommended its use in non-severe tuberculosis [1]. Although, these modified treatment regimens for drug sensitive-TB (DS-TB) and MDR/RR TB have been described, all these regimens may not be feasible to achieve the targets of End TB strategy in Indian scenario. This article elaborates on the latest regimens recommended by WHO and its applicability to children in India. The treatment regimens to be followed as per the National TB Eradication Programme (NTEP) are also discussed. The WHO Guideline is a guidance document that helps national tuberculosis programmes (NTP) to formulate their protocols as per the epidemiological and technical data specific to their country.

Treatment of Drug-Sensitive TB

Treatment of tuberculosis is biphasic, the intensive phase mainly aims at early rapid killing of the Mycobacteria and reduces infectivity and the continuation phase eliminates residual bacteria and reduces treatment failure. Each drug that forms a part of the regimen has a unique role. Isoniazid (INH) and Rifampicin (R) have sterilizing effect on fast-growing bacteria, Pyrazinamide (PZ) rapidly kills the intracellular organism and Rifampicin kills the extracellular organism. Ethambutol (E) is added in areas where INH resistance is high. These 4 drugs constitute the intensive phase. Fewer drugs are required to kill the residual bacteria in continuation phase. In our country, HR and E are given in continuation phase in all new cases. Patients are no longer classified as New or Previously treated and the former category 2 has been removed from treatment protocol. It is advised to investigate the slow responders or non-responders for drug resistance. There is no role of extension of the intensive phase in these cases. In case of mono/polyresistance to any first line drug, different treatment regimen is selected (outlined in drug resistant TB section). The NTEP treatment regimen for DS-TB are outlined in table 1[2].

WHO updated the treatment guidelines in 2022 and made new recommendations based on the SHINE trial[1]. SHINE trial was a non-inferiority trial that compared a 4-month short regime (2HRZE/2HR) with a 6-month regime (2HRZE/4HR) in children less than 6 years of age with non-severe pulmonary tuberculosis (PTB). The 4-month regime was found to be non-inferior and was therefore recommended in children if non-severity of PTB can be adequately determined. Non-severe PTB was defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non- cavitary disease confined to one lobe of the lungs and without a miliary pattern. Although the SHINE trial could demonstrate non-inferiority of the 4-month regime, the outcomes measured were the undesirable effects like treatment failure, treatment lost to follow up, TB recurrence and death. Therefore, it was advised not to favour the longer or shorter regime. However, the cost of treatment would reduce markedly with the shorter regime [3]. In infants less than 6 months of age, children with severe PTB, smear positive pulmonary TB, extrapulmonary TB, standard 6-month regime can be given. The WHO recommended treatment regimens for drug sensitive TB are detailed in Table 2. In adolescents more than 12 years of age, a 4-month short regime consisting of Isoniazid, Rifapentine(P), Moxifloxacin (M) and Pyrazinamide(Z) is conditionally recommended by WHO. A randomized controlled trial was conducted to compare the HPZM and HRZE regimens. This trial was prematurely terminated and only 62 participants were given the HPZM regimen. Tolerability and safety of the regimen could not be assessed. This regime has thus, not been adopted by the NTEP in India [4].
WHO recommends a 12-month regime for management of tubercular and osteoarticular tuberculosis consisting of 4 drug regime (2HRZE) for 2 months followed by 2 drug regime (10HR) for 10 months. However a shorter intensive regimen of 6 months (Isoniazid, Rifampicin, Pyrazinamide and Ethionamide) is also conditionally recommended in children with TB meningitis without any suspicion of MDR-TB[3].

When we consider these WHO recommended shorter regimens in Indian context, India has a high level of INH resistance, high HIV prevalence and certain technical implementation issues that prohibit us from incorporating this strategy in our national program. The shorter regimen cannot be given in severe acute malnutrition, people living with HIV (PLHIV), previously treated patients with anti-tubercular drugs (ATT) for more than 1 month, children with severe pulmonary TB. In India this is a substantial number. In light of the increased risk of grade 3-4 adverse events, increased mortality with shorter regime demonstrated in the SHINE trial, the advisory body in NTEP does not recommend the shorter regime for DS-TB in India[2]. One of the prerequisites for the shorter-regime is that “non-severe” TB must be clearly defined in the patient. Low availability of good quality chest Xray, insufficient capacity for interpretation at lower levels of health care system restricts its use in India.

Treatment of Drug Resistant Tuberculosis

Drug resistance is an emerging and startling issue in the face of achieving elimination of of tuberculosis. Prevalence of MDR-TB in India is estimated to be about 2.8% (2.3–3.5) among new cases and 14% (12– 17) among the previously treated patients[5]. Although second line drugs for treatment of drug resistance TB are available and newer drugs have emerged in

controlling DR-TB, tolerability and availability issues persists. The regimen is usually tailor-made based on the first line-Line probe assay (FL-LPA) and second line-line probe assay (SL-LPA) results and strict monitoring for adverse events is required. The choice of drug is based on the resistance pattern, tolerability history, contraindication (if any) and availability of the drugs.

WHO has divided second line drugs in to three groups based on their efficacy and experience of use (Table 3) and the treatment regime is formulated based on these groups. In MDR-TB patients, all three group A and one or more group B drugs should be included to ensure that at least four TB drugs likely to be effective are given. If group A and group B drugs alone cannot form a regime, drugs from group C can be included to complete the regime[1]. NTEP has formulated regimens based on these principles.

MDR/RR-TB treatment regimens for pediatric age group are described in Table 4. Injectable second line drugs (aminoglycosides) have been removed from regime as hearing loss was difficult to detect in children and could have a devastating effect on cognitive and language development, education and socialization[2]. Although WHO has approved use of Bedaquilline and Delaminid in children <6 years of age, the regulatory approval in India is awaited[2]. Use of Bedaquilline in all-oral shorter regime has been conditionally recommended by WHO in patients with confirmed MDR/RR-TB without FQ resistance, non-severe tuberculosis who have not been exposed to second line ATT for more than 1 month. Delaminid is a part of the longer regime for MDR/RR-TB. The standard duration of treatment with Bedaquilline is 6 months although, extension can be done up to 9 months in selected cases. Use of Delaminid beyond 6 months has not been assessed by WHO. [3].

In case of TB meningitis, second line drugs have variable CNS penetration (Table 4). Regimen must be constructed to include atleast 3 drugs with good CNS penetration and further drugs can be added as per the principles described earlier.Levofloxacin/Moxifloxacin, linezolid, cycloserine/terizidone and ethionamide are first choice drugs for TB meningitis[3].

The NTEP treatment Expert Group India has laid down guidelines for treatment of drug resistance tuberculosis in children in accordance with WHO advice. These treatment regimens are described in table 5. Under the Pediatric TB management guidelines 2022 developed by NTEP, a shorter regime for MDR/RR-TB consisting Bedaquiline along with other second line drugs can be given in children >5 years of age, with Pulmonary TB (except extensive disease), non-severe EPTB, with no previous history of exposure to second-line drugs in the regime for more than 1 month. Extensive pulmonary TB is defined as bilateral cavitatory involvement or extensive parenchymal damage on chest radiography. Severe EPTB is defined as miliary TB or CNS TB. In children > 5 years of age who do not satisfy the inclusion criteria of short-regime, a longer Bdq-containing regime of 18-20 months is given. In children <5 years of age where Bdq or Delaminid is not yet approved, longer regime can be modified by replacing Bdq with a Group C drug[2].

Treatment of Isoniazid Mono/Poly DR-TB

When a patient is found to be INH resistant but R sensitive, the following regime can be started after FL-LPA results. The regime can then be modified based on the SL-LPA report [2].

6 Lfx R E Z

In case of further resistance to second line drugs on SL-LPA, the following protocol can be used to modify or replace drugs in the original regime. (Table 6)

Important Point to Remember while treating a DR-TB case

- Empirical treatment of tuberculosis with anti-TB drugs is not to be done.
- Vigilantly monitor a patient for possible adverse effects of the drugs included in the regime.
- Drug dosages in children may need regular modification as the child gains weight. Shift the patient to higher weight band as the weight limit is crossed.
- Clavulanic acid has to be given along with a carbapenem only, it is not considered an individual agent in second line anti-TB drugs.
- Seizures may be more common in patients of TB meningitis treated with Imipenem. Meropenem is thus, preferred for TB meningitis in children.
- Injectable drugs are to be avoided in children to reduce the risk of hearing loss. However in certain circumstances injectable aminoglycosides may need to be administered. In such cases regular monitoring must be done.
- Slow response or no response to any regime must be actively investigated by nucleic acid amplification test (NAAT) and drug sensitivity testing (DST) on appropriate samples. Extension of therapy may be considered in such situations.
- Never add a single drug to a failing regime as this can lead to amplified resistance to previously sensitive drugs.

References:

1. WHO Consolidated Guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents; 2022
2. Central TB Division, Ministry of Health and Family Welfare; Pediatric TB Management Guideline 2022 developed by National Tuberculosis Elimination Programme. Accessed on September 27, 2022.
3. WHO Operational Handbook on tuberculosis Module 5: Management of tuberculosis in children and adolescents
4. Conde MB, Mello FC, Duarte RS, Cavalcante SC, et al.. A Phase 2 Randomized Trial of a Rifapentine plus Moxifloxacin-Based Regimen for Treatment of Pulmonary Tuberculosis. PLoS One. 2016 May 9;11(5):e0154778. doi: 10.1371/journal.pone.0154778. eCollection 2016.
5. 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 27, 2022. Available from: *www.tbcindia.gov.in*

Newer Anti-TubercularDrugs

Prof (Dr) Sangeeta Sharma
Head of Dept of Pediatrics
Natiional Institute of Tuberculosis and Respiratory Diseases
New Delhi-110030

Emergence of various drug resistant (DR-TB) strains of *Mycobacterium tuberculosis*, namely rifampicin resistant (RRTB), multidrug-resistant (MDRTB) and pre-extensively drug-resistant (PreXDRTB) and extensively drug resistant tuberculosis (XDRTB) has always posed clinical challenges in the management of these patients. Further, the drug resistant disease has always been associated with insufficient therapeutic response to standardized anti-tuberculosis treatment regimens being used and a higher mortality rate. This necessitated research for newer molecules with anti-tubercular activity which had not been used in the past. Two newer drugs which emerged as the front runners in the treatment of drug-resistant tuberculosis are Bedaquiline (Bdq) and Delamanid (Dlm).

As per the recent WHO Consolidated Guidelines for management of TB in children and adolescents (Module-5) -2022 (1) and supporting WHO Operational Handbook (2), use of these newer drugs Bedaquiline and Delamanid is now recommended as a part of combination regimens in children of all ages with DR-TB (RR/MDR/PreXDR/XDRTB) (*conditional recommendation, very low certainty of evidence*).This recommendation is primarily based on various studies in adults highlighting the good efficacy and low adverse drug effects (ADE) of these newer drugs (*strong recommendation, moderate certainty in the estimates of effect*)(3). The same has been extrapolated in recommending the use of these drugs for children and adolescents as the data for ADE in children still remains limited (1,2).

Data of use in children:

Since Bdq became available, some clinicians used it in paediatric MDR-TB patients where only limited treatment options were available. It showed good treatment responses, with no discontinuations due to AEs.(4) Trials, the TMC207-C211 trial and IMPAACT P1108 for Bdq (5) and OPC-67683 (6) trial and a phase I/II trial for Dlm (7) were conducted on children and adolescents. These trials were to meant to evaluate the PK, safety, tolerability and anti-mycobacterial activity of Bdq and Dlm respectively in combination with background regimen drugs for the treatment of clinically diagnosed or bacteriologically confirmed pulmonary (intra-thoracic) and selected forms of extrapulmonary MDR-TB cases.(5, 6,7) TMC207-C211 was a phase II, open-label, single-arm study on children and adolescents 0–17 years of age while IMPAACT P1108 was a phase I/II dose finding de-escalation study in HIV-infected and HIV-uninfected children of bedaquilline.(5) Based on these trials, the TMC207-C211 trial and IMPAACT P1108 trial for Bdq[5] and OPC-67683 trial (6) and a phase I/II trial for Dlm (7), the efficacy data for Bdq and Dlm emerged as 75% and 74.2% respectively. These trials and further studies also showed that Bdq and Dlm were fairly safe in children with few adverse event (AE) related discontinuations or serious AEs and no QTcF >460 ms although some dose modification was required depending on the age and weight of the children. Most importantly, there were significantly fewer episodes of treatment failure, relapse and death (5-9). Further, an IPD meta-analysis showed that second-line injectable drugs (SLI) were associated with irreversible ototoxicity resulting in delayed mental development.(10) Hence, the use of SLI was deprioritised in the recent WHO guidelines in favour of all oral regimens containing the newer drugs, Bdq and Dlm for all forms of DRTB in children of all ages.(1,2)

Bedaquiline (Bdq)

Bedaquiline is a diarylquinoline strong anti-mycobactericidal and sterilizing drug which improves the time to culture conversion in MDR-TB patients. Following oral administration, it is bound to the plasma proteins, widely distributed in the body and metabolized by the liver. It has an extended half-life, remains in the plasma for upto 5.5months after stopping the drug. It is available as 100mg non dispersible and 20mg scored dispersible tablet. (1) Findings from the Bdq crush study showed that the bioavailability of Bdq tablets crushed suspended in water remains the same as for tablets swallowed as whole. (11)

Mechanism of action

Bedaquiline inhibits the proton pump of mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in the mycobacterium resulting in mycobacterial cell death. Mycobacterial resistance to Bdq has been reported and may develop due to a mutation in pepQ (encoding a putative Xaa-Pro aminopeptidase) and Rv1979c (encoding a putative permease). (1)

Indication

Bedaquiline is currently a Group A drug, recommended by the WHO to be used in children of all ages with pulmonary and/or extra pulmonary drug resistant tuberculosis (RR/ MDR/ Pre-XDR/XDRTB) as part of combination regimens, the standardized all oral shorter regimen, Group A drug for individualized longer regimen and in BPaL regimen consisting of Bdq, pretomanid (Pa) & linezolid (Lzd) for select group of patients under operational research mode. (1) Doses are given as per body weight daily for 2 weeks, followed by thrice a week for another 22 weeks, with a total treatment duration of 24 weeks. (table-1) Bdq can be extended beyond 6 months to a maximum 8 months as Off label use for non responder culture positive difficult to treat patients. (1,2,4)

The medicines used in the standardized all-oral Bdq-containing regimen have been part of MDR/RR-TB regimens for many years, in similar combinations, for adults and children, except for Bdq, which was first recommended for use in adults in 2016 and in children aged over 6years in 2019. In India, under the National TB Elimination Program (NTEP), it is approved at present for children > 5years and > 15kg body weight. (12)

Standardized shorter all-oral bedaquiline-containing regimen of 9–11 months duration recommended in eligible patients (1,2,12,13), i.e. with non-extensive PTB and EPTB (peripheral TB lymphadenopathy or isolated mediastinal mass without compression) (13) with confirmed multi–drug or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB drugs used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty in the evidence),* is summarized as follows:

4–6 Bdq(6)–Lfx–Cfz–Z–E–H^h–Eto / 5 Lfx–Cfz–Z–E

Individualized longer regimen is prescribed in children and adolescents with advanced or severe forms of the disease (1,2,12,13) namely, PTB i.e. cavities or bilateral disease, miliary TB on CXR, and severe EPTB i.e. TBM, disseminated disease, extra pulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression). (13) The longer regimen should also be used in those who have been exposed to more than 1 month treatment with second-line TB drugs used in this regimen, intolerance to any drug in the shorter MDR TB regimen or risk of toxicity from a drug in the shorter regimen (e.g. drug–drug interactions), in the presence of resistance to fluoroquinolones, mutations in both the inhA promoter and katG on first-line LPA (MTBDRplus) which indicates that both isoniazid at high dose and ethioamide are not effective.(1,2,12).

Concomitant use of Bdq and Dlm can be given in children in special situations, as part of Individualized longer regimen based on DST when other treatment options are limited. (1,2).

Inclusion criteria

- children aged >5 years and weighing at least 15kg (12).
- Patients with controlled stable arrhythmia after obtaining cardiac consultation
- QTcF < 450 ms in males and <470 ms in females at baseline (QT is corrected for heart rate, referred to as the QTc and with fridericia correction (QTcF) is calculated by most ECG machines). Values of QTcF more than 450msin male and 470ms in female are referred to as prolonged. Patients with prolonged QTcF are at risk for developing cardiac arrhythmias like torsades de pointes, which can cause sudden death. Currently, ECG monitoring prior to initiation and during DR-TB treatment is only required with the use of Bdq or when twodrugs known to prolong QTcF (e.g. Mfx, Cfz) are combined in the same regimen.
- Normal serum potassium, calcium and magnesium at baseline as low serum levels of K, Ca, Mg are associated with QTc prolongation. Levels need to be corrected before initiation.
- No history of structural cardiac abnormalities (LVH or RVH secondary to hypertensioncan also cause ECG changes, however mere presence of LVH need not be an exclusion criteria) or ECG abnormalities
- Patients with QTcF between >450 to 500 ms in male and > 470 to 500 ms in female require daily monitoring of ECG for 3 days along with evaluation and correction of any electrolyte abnormalities. A cardiologist opinion may need to be taken.

Exclusion criteria

- Having uncontrolled cardiac arrhythmia despite medication.
- With any of the following:
- QTcF interval characteristics at screening: QTcF >500 at baseline with normal electrolytes. ECG is repeated after 6 hours and if both ECGs show QTcF >500 then the patient should not be challenged with cardiotoxic drugs; and
- History of additional risk factors for Torsade de Pointes, e.g. heart failure, family history of long QT syndrome.
- Hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to a patient receiving any QTc prolonging drugs.

Adverse effects (1,2,12)

>10%

*Nervous system : Headache
*Cardiovascular – Chest pain
*Respiratory – Hemoptysis
*Gastrointestinal – Nausea, other GI symptoms.
*Neuromuscular and Skeletal – Arthralgia
*Hepatic – Raised Serum transaminases

1-10%

*Gastrointestinal – Anorexia
*Dermatologic – Skin rash

<1%

*Hepatotoxicity and prolonged QT interval on ECG.
*Pancreatitis

The following medications are not allowed during the 24-week administration of Bdq and up to one month after the last dose of Bdq because of potential drug–drug interactions:

- Systemic use of moderate and strong CYP3A4 inhibitors, e.g. azole antifungals:ketoconazole, voriconazole, itraconazole, fluconazole; ketolides such as telithromycin and macrolide antibiotics other than azithromycin for > 2consecutive weeks;
- Systemic use of strong CYP3A4 inducers,
- e.g.phenytoin, carbamazepine, phenobarbital;
- Rifamycins (rifampin,rifabutin,rifapentine);and
- Cholesterol lowering medications :“statin”class.

Bdq should be used with caution in CLHIV infection treated with ARVs that exhibit drug-drug interactions with Bdq (efavirenz) or prolong the QT interval (lopinavir/ ritonavir) as well as in patients with comorbidities (such as diabetes). Frequent clinical and cardiac evaluation is required in these patients.

Delamanid (Dlm)

Delamanid is a nitro-dihydro-imidazo-oxazole with anti-mycobacterial activity. It has a half-life of 36hours. Delamanid is a relatively newer drug that has exhibited potency against both drug-susceptible and drug-resistant strains of *Mycobacterium tuberculosis*.

Mechanism of action

The anti-mycobacterial activity is due to two different mechanisms of action. Upon oral administration, delamanid, a pro-drug, is activated and inhibits mycolic acid synthesis of bacterial cell wall causing cell death. It also releases nitric oxide which is toxic resulting in death of the mycobacteria.

Mycobacterial resistance to delamanid has been reported and develops due to a mutation in one of the five coenzyme F420 genes necessary for the activation of delamanid.

Indication

As per WHO, Dlm is currently a Group C drug recommended to be used in children of all ages to treat MDR/RR-TB as part of the individualized longer regimen [1,2] while in India, Dlm has been recently approved for use in infants and children weighing >10 kg body weight. (12) (table-1)

Adverse effects[1,2,12]

>10 %

*Nervous system – Headache,dizziness,parasthesia and insomnia.
*Gastrointestinal – Nausea,vomiting,gastritis,diarrhea,GI discomfort.
*Hematologic – Reticulocytosis.
*Neuro muscular and skeletal : Arthralgia,myalgia,tremor.

1-10%

*Nervous system – Agitation, Anxiety, depressed mood,psychosis,hypoaesthesia.
*Cardiovascular – Prolonged QT interval on ECG,palpitations,flushing,hypertension,peripheral edema,chest discomfort.
*Respiratory - -Cough,dry throat, dyspnea,oropharyngeal pain,rhinorrhea,throat irritation.
Endocrine and Metabolic Disorders – Hypertriglyceridemia and increased cortisol levels.
*Hematologic and oncologic: Anemia, eosinophillia, and hematoma.
*otic- otalgia

<1%

Dysphagia, dysphoria,dysuria,abdominal tenderness,aggressive behaivior,decreased cortisol,pancreatitis,hypercholesterolemia,hypokalemia,nerve root disorder etc.

Special considerations for use of Bdq and Dlm:

Since these drugs havesignificant adverse effects, a pre-treatment evaluation is imperative to rule out any underlying co-morbid conditions, ECG or biochemical derangements is essential. The first dose should be given under supervision at the health facility for ambulatory patients. Bdq and Dlm should be taken after a light meal alongwith other anti-TB drugs, patients should not consume milk containing products at the same time, as the calcium in these can decrease the absorption of FQs; and large fatty meals should be avoided, as these can impair absorption of some of the other anti-TBdrugs (Cs,H etc.).

All doses are to be supervised by the treatment supporter. Empty blisters of drugs taken unsupervised in the evening and on Sundays are to be collected by treatment supporter.

No dosage adjustments required in patients with mild to moderate renal impairment (in severe renal impairment, use with caution). Data on the CNS penetration of Bdq or Dlm is still emerging,

Other second-line drugs that are likely to be administered with Bdq/ Dlm, notably FQs and Cfz may potentially increase the risk of cardiotoxicity.

Table 1: WHO Recommended Doses of BDQ & DLM (as per body weight) (1,2)

Medicine	**Formulations (mg/mL, as applicable)**	**Weight bands[a]**								**Usual upper daily dose[b]**	**Comments**
		3 to <5 kg	**5 to <7 kg**	**7 to <10 kg**	**10 to <16 kg**	**16 to <24 kg**	**24 to <30 kg**	**30 to <36 kg**	**36 to <46 kg**		
Bedaquiline	20 mg dt[e]	0 to <3 months: 1.5od for 2 weeks; then 0.5 od M/W/F for 22weeks ≥ 3 months: 3 od for 2 weeks; then 1 odM/W/F for 22 weeks	0 to <3 months: 1.5od for 2 weeks; then 0.5 od M/W/F for 22 weeks ≥ 3 months: 3 od for 2 weeks; then 1 odM/W/F for 22 weeks	0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F for 22 Weeks 3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks ≥ 6 months: 4 odfor 2 weeks; then2 od M/W/F for 22 weeks	3 to <6 months:3 od for2 weeks; then 1 od M/W/F for 22 weeks ≥ 6 months: 6 od for 2 weeks; then 3 od M/W/F for 22 weeks	10 od for 2 weeks; then 5 od M/W/F for 22 weeks	10 od for 2 weeks;then 5 od M/W/F for 22 weeks	20 od for 2 weeks; then 10 od M/W/F for 22 weeks	20 od for 2 weeks; then 10 od M/W/F for 22 weeks	-	A daily loading dose is used for the first 2 weeks, followed by a maintenance dose given three times a week
	100 mg tab[e]	0 to <3 months: 3 mL od for 2 weeks;then 1 mL od M/W/Ffor 22 weeks[c] ≥ 3 months: 6 mL od for 2 weeks; then2 mL od M/W/F for 22 weeks[c]	0 to <3 months: 3 mL od for 2 weeks;then 1 mL od M/W/F for 22 weeks[c] ≥ 3 months: 6 mL od for 2 weeks; then2 mL od M/W/F for 22 weeks[c]	0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F for 22 weeks[c] 3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F for 22 weeks[c] ≥ 6 months: 8 mL od for 2 weeks; then 4 mL od M/W/F for 22 weeks[c]	3 to <6 months: 6 mL od for 2 weeks; then 2 mLod M/W/Ffor 22 weeks[c] ≥ 6 months: 12 mL od for 2 weeks; then 6 mLod M/W/Ffor 22 weeks[c]	2 od for 2 weeks; then 1 od M/W/F for 22 weeks	2 od for 2 weeks;then 1 od M/W/F for 22weeks	4 od for 2 weeks; then 2 od M/W/Ffor 22 weeks	4 od for 2 weeks; then 2 od M/W/Ffor 22 weeks	-	
Delamanid	25 mg dt[j]	1 od	<3 months: 1 od	<3 months: 1 od ≥ 3 months: 1 bd	1 bd	2 morning 1 evening	2 morning 1 evening	2 bd	2bd	-	

			≥ 3 months: 1 bd								
	50 mg tab [j] (50 mg in 10 mL = 5 mg/mL)	5 mL (0.5 tab)od [c]	<3 months: 5 mL (0.5 tab)od [c] ≥ 3 months: 5 mL (0.5 tab)bd [c]	<3 months: 5 mL (0.5 tab)od [c] ≥ 3 months: 5 mL (0.5 tab)bd [c]	5 mL (0.5 tab)bd [c]	10 mL (1 tab) morning 5 mL (0.5 tab) evening	10 mL (1 tab) morning 5 mL (0.5 tab)evening	1 bd [k]	1 bd [k]	-	

Conclusion:

Bedaquiline and Delamanid are strong anti-mycobactericidals and game changers in the management of DRTB in children. These are fairly safe in children,decrease episodes of treatment failure, relapse and DRTB deaths.

Monitoring of patients is required for cardiac dysrhythmias or QT interval prolongation, for electrolyte imbalances (especially serum potassium). Also care should be taken in patients with renal impairment, pre-existing liver disease, seizure disorders and psychiatric illnesses.

References:

1. WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022.

2. WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022.

3. WHO consolidated guidelines on tuberculosis. Module4: treatment-drug-resistant tuberculosis treatment. Online annexes. Geneva: World Health Organization; 2020 (https: //apps. who.int/ iris/ handle/10665/332678, accessed 5th October 2022).

4. Achar J, et al. Off-label use of bedaquiline in children and adolescents with multidrug-resistant tuberculosis. *Emerg Infect Dis.* 2017; 23: 1711–1713.

5. Moodliar R, Aksenova V, Frias MVG, et al. Bedaquiline for multidrug-resistant TB in paediatric patients. Int J Tuberc Lung Dis. 2021; 25:716-724.

6. Sotgiu G, Pontali E, Centis R, et al. Delamanid (OPC-67683) for treatment of multi-drug-resistant tuberculosis. Expert Rev Anti Infect Ther. 2015; 13: 305-315.

7. Garcia-Prats AJ, Frias M, van der Laan L, et al. Delamanid Added to an Optimized Background Regimen in Children with Multidrug-Resistant Tuberculosis: Results of a Phase I/II Clinical Trial. Antimicrob Agents Chemother. 2022; 66: e0214421.

8. Li, Yang et al. "Bedaquiline and delamanid in the treatment of multidrug-resistant tuberculosis: Promising but challenging." *Drug development research.*2019; 1: 98-105.

9. D'Ambrosio L, Centis R, Tiberi S, et al. Delamanid and bedaquiline to treat multidrug-resistant and extensively drug-resistant tuberculosis in children: a systematic review. J Thorac Dis. 2017;9: 2093-2101.

10. Harausz EP, Anthony J, Law GPS, et al. Treatment and Outcomes in Children with Multidrug-Resistant Tuberculosis: A Systematic Review and Individual Patient Data Meta-Analysis 2018. *PLoS Med* 2018;15(7): e1002591. https://doi.org/10.1371/journal.pmed.1002591

11. Svensson EM, du Bois J, Kitshoff R, et al. Relative bioavailability of bedaquiline tablets suspended in water: Implications for dosing in children. Br J Clin Pharmacol. 2018; 84: 2384-2392.

12. Guidelines for programmatic management of Drug resistant TB in India 2021

13. Wiseman CA, Gie RP, Starke JR, et al. A proposed comprehensive classification of tuberculosis disease severity in children. Pediatr Infect Dis J.2012; 3: 347-352.

Management of Pneumothorax in Child with Tuberculosis-A Learning Case

Sheetal Agarwal, MD, Kanaram Jat, MD, Sushil K Kabra MD, DNB
Department of Pediatrics, AII India Institute of Medical Sciences, New Delhi

Abstract: Spontaneous pneumothorax secondary to tuberculosis is relatively rare in children. It generally occurs in adults due to extensive lung involvement or cavitary lesion. Management of recurrent pneumothorax is challenging as antitubercular therapy and intercostal drainage alone may not be sufficient. Here we describe a case of 6-year-old girl who presented as spontaneous pneumothorax and diagnosed to have multidrug resistant TB. The pneumothorax was non-resolving with waxing and waning periodand not amenable to intercostal drain alone. Chemical pleurodesis with povidine iodine solution was done which resulted in complete recovery.

Tuberculosis is one of the commonest infective diseases in our country. It poses a diagnostic challenge due to its paucibacillary nature in children. Many a times it directly presents as a complication to underlying tubercular pathology. Spontaneous pneumothorax secondary to tuberculosis is one such complication which is relatively uncommon even in adult patients and extremely rare in children. We present a case of small girl who presented as spontaneous pneumothorax and was diagnosed to have multidrug resistant TB. The child had non- resolving pneumothorax with waxing and waning period which was challenging to manage.

Case Summary:

A 6-yr-old girl presented to us with history of fever for 2 months and fast breathing for 15 days. The fever was high grade in the range of 102–104^0 F initially. It was also associated with chills, rigors and sweating and used to respond to antipyretics. Fever gradually decreased in intensity and frequency with treatment taken locally. Child remained afebrile for 15 days and then again had a recurrence of fever which was of low intensity. Along with fever she also had respiratory distress in the form of fast breathing, retractions and dyspnea. Child was again treated locally with injectable medications. However, there was no improvement and hence was referred to government hospital in Delhi. There was no history of pedal edema, orthopnoea, palpitations which would suggest cardiac etiology. There was no history of documented weight loss or contact with tuberculosis (TB) patient. There was no history suggestive of flu like illness or contact with Covid patient and no exposure to avian antigens or history of recurrent nebulization in past.

The chest x-ray done in the previous hospital showed right sided pneumothorax, along with miliary shadows in lung parenchyma (Figure 1). Intercostal drain (ICD) was inserted and the child was started on first line anti tubercular therapy (ATT) based on clinic-radiological basis as the first gastric aspirate for gene Xpert was negative. Even after ICD insertion there was non-resolution of pneumothorax for which ICD insertion and repositioning was required on multiple

occasions. The child was then referred to our institute for further management. At admission to our institute, she was hemodynamically stable with respiratory rate of 48/min and mild subcostal and intercostal retractions. The saturation was 99% on oxygen by nasal prongs at 2l/min. The general physical examination was unremarkable except for presence of mild pallor. There was no clubbing. The height, weight and BMI were also within normal limits (< 2 SD).

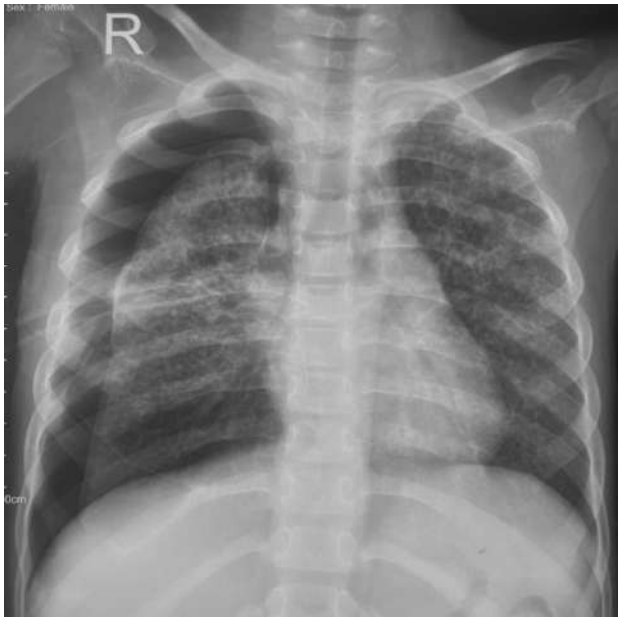

Figure 1: Chest radiograph showing fine reticulonodular shadows with right pneumothorax

On respiratory system examination**,** the trachea shifted towards right side with decreased movement of chest on right. There was resonant note all over chest field except in right side axillary and infra axillary where hyperresonant note present. On auscultation air entry was absent in right axillary and infra axillary areas with increased vocal resonance on right side. There were no crepitations or rhonchi. The ICD tube was in situ on right side with rapid column movement and bubbling on coughing. Other systemic examination was unremarkable except for pushed down liver.

Contrast-enhanced CT chest was reviewed which was suggestive of mediastinal lymphadenopathy (right paratracheal, subcarinal, right hilar- necrotic nodes, largest node measuring 1.9x 1.2 cm in right paratracheal location). There were multiple cysts in lung parenchyma in bilateral upper lobe with centrilobular nodules, along with pneumopericardium, pneumomediastinum and right hydropneumothorax (Figure 2 & 3). Radiological possibilities of tuberculosis, Langerhans histiocytosis, Pneumocystis jirovecii pneumonia and post COVID sequalae were kept.

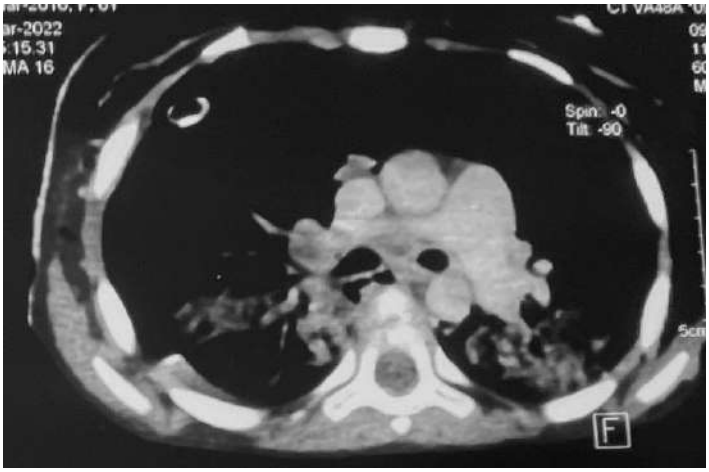

Figure 2: Contrast enhanced CT Chest showing multiple necrotic mediastinal lymph nodes

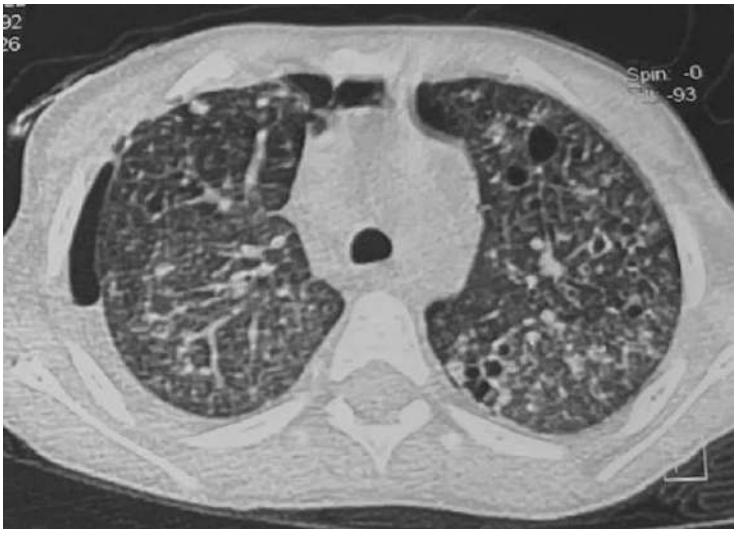

Figure 3: Contrast enhanced CT Chest showing multiple cysts in bilateral upper lobe with centrilobular nodules

As there was very high suspicion of TB, a repeat Trunaat was sent which came positive for MTB complex and showed rifampicin resistance. Hence the child was started on 2nd line ATT. However, respiratory distress and rapid column movement in ICD tube along with bubbling persisted which suggested broncho-pleural fistula (BPF) with persistent pneumothorax. So we planned to localize BPF and repair it with either endobronchial glue injection or surgically. In the next few days, the column movement gradually reduced and bubbling stopped, indicating a spontaneous resolution of BPF. However, pneumothorax persisted, suggesting loculated pneumothorax. Hence a repeat CT guided pigtail insertion was done. Within 1-2 days, the pneumothorax resolved and the respiratory distress also subsided. As there was a high likelihood of recurrent pneumothorax due to underlying cavitary lesions which could prove fatal,

pleurodesis was done with povidine iodine once the lung had completely expanded. Post pleurodesis, the child was stable, pigtail was removed after 2 days and repeat chest x ray showed complete expansion of the right lung (Figure 4). There was no recurrence of pneumothorax subsequently.

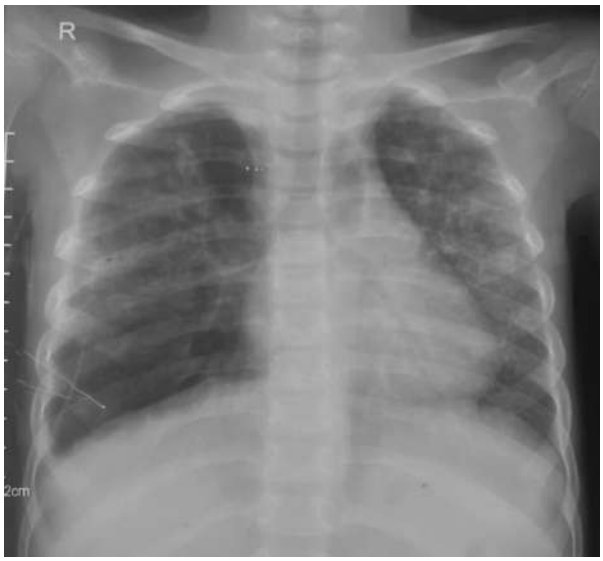

Figure 4: Post pleurodesis resolution of pneumothorax

Discussion:

TB is one of the commonest infectious diseases in our country. The incidence of TB in children is approximately 3 lakhs/year in our country and accounts for about 6% of all total TB cases(1). Spontaneous pneumothorax secondary to TB is rare with an overall incidence ranging from1.5%-5% (2,3). The exact incidence in children is not known due to its rare occurrence. Secondary pneumothorax in TB generally occurs in young adults with cavitary lesions. The basic pathophysiology is extensive lung involvement due to TB causing formation of pneumatoceles followed by rupture into pleural space or cavitary lesions or rarely due to caseation or necrosis of subpleural miliary nodules(4,5). In children, it is generally associated with miliary TB in small children or cavitary TB in adolescent age group. The pneumothorax associated with TB can be life threatening due to underlying parenchymal pathology and is associated with high mortality in adults. The mortality rate was reported to be 33% in a study by Yagi et al (6). In most of the adult patients (42-50%), pneumothorax was the initial presentation and TB was diagnosed later as in our case (3,6). Therefore, TB should be suspected in cases of secondary pneumothorax with no obvious etiology.

The mainstay of management of secondary pneumothorax in TB is ATT and intercostal tube drainage of pneumothorax along with supportive care. It usually resolves by this management, however in rare instances further interventions have to be done as in our case. Management of recurrent/non-resolving pneumothorax in children is challenging and comprises of minimally invasive techniques to open surgery. Hulme et al reported a case of spontaneous pneumothorax

in a 2-year-old requiring ICD insertion with complete resolution of pneumothorax(7). Many adult patients require surgical intervention like open thoracotomy or video assisted thoracoscopy in addition to ICD (3,6,8).

Pleurodesis is a procedure undertaken to create the symphysis between the parietal and visceral pleura in order to eliminate the pleural space. The major indications of pleurodesis are to prevent the recurrence of spontaneous pneumothorax or pleural effusion. The two major methods that can be used to achieve pleurodesis are: 1) direct injury to the pleura with mechanical or physical methods (e.g. mechanical abrasion, laser or argon beam coagulation) during video-assisted thoracoscopic surgery (VATS) and 2) intrapleural administration of various agents (e.g. talc, bleomycin, tetracycline, iodopovidone, autologous whole blood) that induce formation of pleural adhesions. Chemical sclerosants can be administered in the pleural space by a pleural catheter or single point entry medical thoracoscopy. Chemical pleurodesis is less invasive procedure than VATS and is more commonly used. The efficacy rate of various sclerosants is different. Talc is an effective sclerosing agent, easy to use, easily available, cheap and relatively free of side effects. The efficacy rate is between 78-96%(9). Autologous blood pleurodesis involves immediate administration of 50-150 ml of autologous venous blood without coagulants into the pleural cavity through pleural drainage. It has dual mechanism of action. The air leak gets directly sealed by the formation of a clot and fibrogenic activity of blood creates pleurodesis via pleural irritation and inflammation as against tetracyclines and talc which only produce inflammation and scarring with no 'patch' effect, hence time taken to pleurodesis is shorter with autologous blood. The efficiency rate is between 75%-84% with recurrence rates of 0-29%(10). Povidone iodine is also easily available, inexpensive, safe and effective antiseptic solution (11,12). The efficiency rate is 94% in the treatment of spontaneous pneumothorax(13). Adverse effects include pleuritic pain (13%-18%), hypotension, fever, empyema and acute respiratory distress.

Thoracoscopic pleurodesis and bedside methods of chemical pleurodesis successfully prevent the recurrence of primary and secondary spontaneous pneumothorax. Thoracoscopy allows for simultaneous inspection and resection of subpleural blebs and bullae. Mechanical plus chemical pleurodesis has been found to be more effective in recurrence of pneumothorax than mechanical pleurodesis alone. Our patient was successfully treated with chemical pleurodesis with povidine iodine without any further recurrences.

Conclusion: Spontaneous pneumothorax is a rare complication of tuberculosis. Although miliary pattern on chest X-Ray has several differentials but TB still remains first differential diagnosis in children in our country. Children with miliary TB are generally sick and may present with complications. Thorough investigations to confirm microbiological diagnosis of TB is essential as it may identify DRTB and has treatment implications. Pleurodesis may be tried in recurrent/non-resolving spontaneous pneumothorax before going for major surgical interventions.

Key Messages

1. Spontaneous pneumothorax is a rare presentation of TB in children but can occur in any drug sensitive or a drug resistant pulmonary TB.
2. A repeat and extensive work up for DRTB is necessary ina case with high suspicion of TB with no response or poor response.
3. Pleurodesis can prevent recurrent pneumothorax in TB patient with multiple cysts which could be life threatening.

References:

1. Central TB Division, 2020. India TB Report - 2020. National Tuberculosis Elimination Program - Annual Report. New Delhi: Central TB Division, Ministry of Health and Family Welfare, Government of India.

2. Aktoğu S, Yorgancioglu A, Cirak K, et al. Clinical spectrum of pulmonary and pleural tuberculosis: a report of 5,480 cases. Eur Respir J. 1996; 9: 2031–2035.

3. Shamaei M, Tabarsi P, Pojhan S, et al. Tuberculosis-Associated Secondary Pneumothorax: A Retrospective Study of 53 Patients. Respiratory Care. 2011; 56: 298–302.

4. Noppen M, De Keukeleire T. Pneumothorax. Respiration. 2008;76: 121–127.

5. Singh AS, Atam V, Das L. Secondary spontaneous pneumothorax complicating miliary tuberculosis in a young woman. Case Reports. 2014; bcr2013201109.

6. Yagi T, Yamagishi F, Sasaki Y, et al. Clinical review of pneumothorax cases complicated with active pulmonary tuberculosis. Kekkaku : [Tuberculosis]. 2002; 77:395–399.

7. Hulme KM, Isaacs D, Marais BJ, et al. Spontaneous Pneumothorax in a Young Child With Pulmonary Tuberculosis. The Pediatric Infectious Disease Journal. 2018; 37: e343.

8. Kwas H, Zendah I, Ghedira H. Spontaneous pneumothorax secondary to tuberculosis. Tunis Med. 2017; 9: 276–279.

9. Lee YC, Baumann MH, Maskell NA, et al. Pleurodesis practice for malignant pleural effusions in five English-speaking countries: survey of pulmonologists. Chest. 2003;124:2229–2238.

10. Manley K, Coonar A, Wells F, Scarci M. Blood patch for persistent air leak: a review of the current literature. Curr Opin Pulm Med. 2012;18: 333-338.

11. Olivares-Torres CA, Laniado-Laborin R, Chavez-Garcia C, et al. Iodopovidone pleurodesis for recurrent pleural effusions. Chest. 2002;122:581–583.

12. Agarwal R, Aggarwal AN, Gupta D. Efficacy and safety of iodopovidone pleurodesis through tube thoracostomy. Respirology. 2006;11:105–108.

13. Agarwal R, Khan A, Aggarwal AN, et al. Efficacy & safety of iodopovidone pleurodesis: a systematic review & meta-analysis. Indian J Med Res. 2012; 135: 297–304.

Case Report

Tubercular Meningitis- The delay can cost you!

Rakesh Dogra DCH

Senior Specialist-SAG,

Department of Pediatrics, Hindu Rao Hospital & North DMC Medical College, Delhi

Abstract: Tubercular meningitis (TBM) is the most dreaded form of tubercular disease in any age group and is associated with lot of morbidity and mortality. The delay in the diagnosis and management can lead to complications and death. This case highlights the importance of identifying the specific hints towards the etiology and early initiation of management to prevent morbidity and mortality. Aggressive initiation of decongestive measures and anti tubercular treatment (ATT) should be started as early as possible. Complete recovery of the deficits on ongoing ATT and anti-inflammatory and decongestive therapy. Detailed history, thorough examination and careful interpretation of lab reports including pointers in chest x ray helps in making the early diagnosis and subsequent decrease in incidence of morbidity and mortality.

Keywords: Tubercular Meningitis, Extrapulmonary tuberculosis, early diagnosis, Chest X-rays

Tuberculosis remains a major cause of morbidity and death from infectious diseases for children of all ages globally, particularly in young children (1). Central Nervous System Tuberculosis (CNS TB) forms the most severe of the extrapulmonary TB. It is common in children < 2 years of age. Children may present with meningitis (95%) or tuberculomas (5%) (2). Early diagnosis and prompt initiation of management is the key to intact survival in TB meningitis case. The case is being reported in view of delay in the diagnosis in spite of the pointers present to the disease.

Case Report

12 year old male child weighing 35 kg presented in the hospital with history of vomiting, headache and fever for last 25 days. Fever followed onset of vomiting and headache by 2-3 days. On examination patient was sick looking with poor general condition and altered sensorium. His vitals were stable and pupils were normal in size & reaction bilaterally. Generalized hypertonia was present with exaggerated deep tendon reflexes. Neck rigidity was present with positive Kernigs and Brudzensikis sign. Left lateral rectal palsy was present. Patient was immediately shifted to ICU in view of low GCS and was put on decongestive measures, antibiotics and history was reviewed.

Patient was apparently well some 25 days back when he developed headache along with vomiting, initially in the early mornings and later on throughout the day. He started having fever 2-3 days after these symptoms. He was given symptomatic treatment from local general practitioner. He was admitted in a private nursing home on non-abatement of symptoms in a drowsy state. His vitals were recorded as normal and doubtful presence of neck rigidity was also recorded. On the day of admission his Hb was 12.9gm%, TLC- 5600/cumm, DLC- P60, L35, E03, M02, B00 and platelets were 3.99 lakhs/cumm.KFT, LFT, Dengue serology, Malaria antigen, Widal test, Typhi Dot and Covid RTPCR were normal. His fundus examination was normal. MRI brain (non-contrast) performed on day 2 of admission was also normal. Chest X-ray was done on day 2 of admission revealed bilateral paratracheal lymphadenopathy but was not reported. No CSF examination was performed. Patient was put on ceftriaxone, mannitol, acyclovir and dexamethasone and was referred to higher centre on attendant's request.

Patient's father came to our hospital for second opinion with chest x-ray and blood reports prior to discharge. The possibility of TB was told to the attendants on the basis of chest x-ray findings of bilateral paratracheal lymphadenopathy (Figure 1) and was advised CSF examination and option of transfer was given.

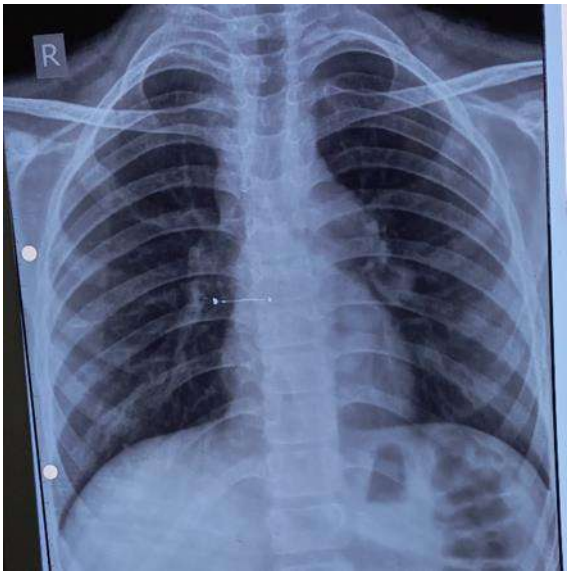

Figure 1. CXR showing bilateral paratracheal lymphadenopathy

Instead of taking the patient to some higher centre, patient was admitted in another small private hospital for next 5 days. Patient developed left lateral rectus palsy. Lumbar puncture was performed and revealed white cell count of 470 cells/cumm, all lymphocytes and sugar and protein of 54 and 107.2 mg% respectively. CSF culture was sterile. No AFB examination and

NAAT were performed on CSF sample. His CBC, KFT, LFT, Urine routine, USG abdomen were all normal during his stay in this hospital. Patient received Inj. Ceftriaxone, Inj. Vancomycin, Inj. mannitol, Inj. dexamethasone, Glycerol during admission. No ATT was started. Patient was referred to higher centre on Day 6 of admission with diagnosis of acute viral meningitis with left medial squint with suspected hydrocephalus.

Patient was brought to our hospital in an altered sensorium with features of raised intra cranial pressure (ICP) and left lateral rectus palsy and was shifted to ICU in view of low GCS and poor general condition. Just before coming to our hospital attendants got a NCCT head (Figure 2) of their own which showed features of hydrocephalus. ATT was started in appropriate dose along with other decongestive measures, intravenous steroids, antibiotics and other supportive measures. His general condition of the child improved within 24 hours and patient was shifted out of ICU on day 4 of admission. Gastric aspirate for CBNNAT was negative. His lateral rectus palsy was persisting however other features of raised ICP subsided gradually and was discharged on Day 14 of admission in a stable condition with persistence of left lateral rectus palsy that subsided completely after 5 months. Lymphadenopathy on chest x-ray that was present at the initial stages also disappeared on x-ray done after 6 months (Figure 3). Patient is currently doing well with adequate weight gain and is on ATT.

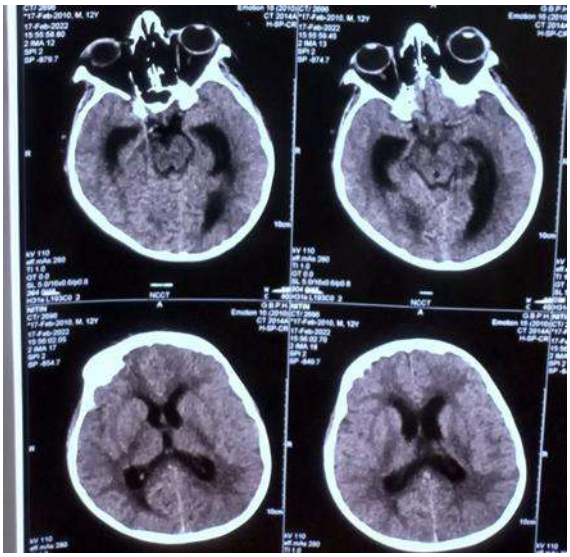

Figure 2. CT head with hydrocephalus

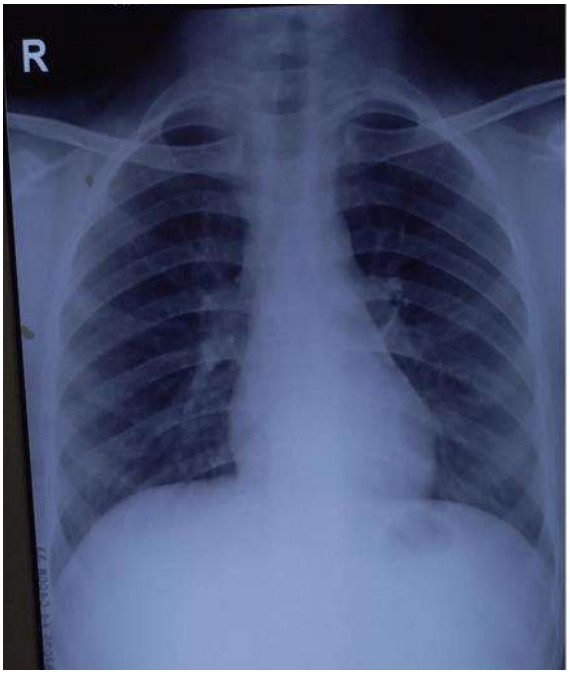

Figure 3. CXR with resolution of lymphadenopathy

Discussion

As per the Global TB Report 2021, about 3.06 lakhs children (0-14 years of age) are estimated to get TB every year. Childhood tuberculosis (TB) constitutes approximately 10%–20% of all TB cases in India, causing almost 8%–20% of TB-related deaths. Twenty-five percent of the pediatric tubercular cases are extrapulmonary, with tubercular meningitis (TBM) being the most common cause of death because of TB. It commonly affects children between 6 months and 4 years of age (3).

Tubercular meningitis (TBM) is a medical emergency. The prompt diagnosis and institution of adequate management measures helps in avoiding significant morbidity and mortality. Any delay in diagnosis and treatment can have grave sequel and outcome including death. Due to suboptimal performance of the diagnostic tests, TBM diagnosis requires vital clinical information coupled with supportive investigations (biochemical, immunological, and radiological) (4).

TBM is the most severe manifestation of TB, leading to high rates of childhood TB mortality, at an average of 19%, and neurodisability in >50% of survivors, even when treatment is provided. The most important predictors of favourable outcome in childhood TBM are early

diagnosis and immediate initiation of treatment (5). Risk factors for TBM include age <5 years, household contact, PEM grade III and IV, recent measles and HIV infection (6).

The onset is usually insidious with irregular fever, malaise, weight loss and anorexia over last few weeks. It is followed by headache, photophobia, and meningism. Infants may have bulging fontanelle. If untreated, the illness progresses to a vasculitic phase, with focal neurological deficits like cranial nerve palsies, hemiparesis often accompanied by seizures with worsening sensorium and coma. Cranial nerve palsies occur in 20–30% cases and are an important pointer to suggest TBM in a case of undifferentiated meningitis (6).

The neurological picture mostly results due to combined effect of increased ICP and infarction. A history of contact is identified in approximately 50 to 60% of children. A close association with disseminated tuberculosis is seen in pediatric age. Cranial nerve palsies occur in 20-30‰ of patients. The sixth cranial nerve is most commonly affected. Vision loss due to optic nerve involvement may occasionally be a dominant presenting illness. Ophthalmoscopic examination may reveal papilloedema and choroid tubercle (7).

CNS is involved following primary infection of the lungs through haematogenous spread to the brain. Initially, small tuberculous lesions known as 'Rich foci' form around the bacteria that are deposited in the brain during bacteraemia of primary TB. These foci located in the subpial or subependymal surface of the brain, meninges and bacilli remain in a dormant state for a prolonged duration. The onset of TBM follows the growth and rupture of these lesions into the ventricular system or subarachnoid space. On an average, TBM occurs 6 to 12 months after the primary infection (8)

Three stages of CNS TB with clinical and prognostic implications have been described. Stage 1 is characterized by nonspecific constitutional symptoms such as fever, headache, irritability and loss of interest in surroundings. Not much clinical signs are appreciated in stage 1. In stage 2, child may progress to lethargy and drowsiness. At this stage clinical examination may reveal signs of meningeal irritation, raised ICP and cranial nerve palsies and seizures. In stage 3, children progress further to coma and other neurological signs like hemiplegia/paraplegia and abnormal posturing. Death or long term sequalae, although uncommon in patients diagnosed at stage I, are seen in 50% and 40% of patients in stage III, respectively (2).

Early diagnosis of TBM is challenging given that, early symptoms are often non-specific therefore requiring high index of suspicion. The various methods used in the diagnosis of TBM include clinical setting of the patient, CSF cellular and biochemical analysis, microbiologic confirmation in CSF and other supportive testing such as neuroimaging and evidence of TB in other parts of the body.

CSF evaluation in TBM shows leukocytosis with lymphocyte predominance, elevated proteins and decrease in CSF glucose levels. A fine clot resembling cobwebs may form due to the presence of very high level of protein in CSF when it is left undisturbed for some time

(8).Our patient had CSF pleocytosis, (470 cells/cumm) with 100% lymphocytes and sugar and protein of 54 and 107.2 mg% respectively and was suggestive of TBM and warranted further evaluation. Further, blood glucose levels done ideally 30 minutes before the CSF sampling or concurrent should have been available to assess the presence of low sugar levels in CSF. A simple smear examination of the fluid for AFB could have confirmed the diagnosis if detected. Few studies have reported that CSF ADA level of 10 U/l or higher with sensitivity of 94.73% and a specificity 90.47% for differentiating TBM from meningitis caused by other infectious agents(8) . However the test is not recommended in National Tuberculosis Elimination Program (NTEP) guidelines. In this case CSF should have been sent for NAAT and one aliquot kept for MGIT later on if required. Almost half of TBM patients may show abnormal chest x-ray. The typical features suggestive of tuberculosis are presence of fibrocavitatory disease, miliary nodules and paratracheal or hilar lymphadenopathy.

The presence of infarcts, hydrocephalus, tuberculomas, basal meningeal enhancement and pre-contrast basal hyperdensities in computed Tomography (CT) scan are suggestive of TBM. Hydrocephalus and meningeal enhancement are important signs of TBM in CT scan, observed in 80 and 75 per cent of children with TBM, respectively. Sensitivity of magnetic resonance imaging (MRI) is more than CT in detecting basal meningeal enhancement, granulomas and infarcts in paediatric TBM (8). Contrast enhanced neuroimaging should be done for better delineation of details as described unlike our case where contrast was not given.

NTEP approved rapid nucleic acid amplification tests (NAAT) like XpertMtb/Rif/CBNAAT and/or Truenat have made it possible to detect Mycobacterium tuberculosis (MTb) with much higher sensitivity as compared to smear and rapidly than culture. The turnaround time for NAAT is 2 hours. These tests are also nested for establishing rifampicin resistance - a surrogate for multi-drug resistant (MDR) TB (9). Sensitivities of smear examination, X-pert and Mycobacteria Growth Indicator Tube (MGIT) culture in TBM patients are reported as 78.6, 59.3 and 66.5% respectively and Gene Xpert's specificity is 99.5% (8). Therefore, it is a good rule in test but a negative test doesn't rule out TBM.

The National Strategic Plan (NSP) for Tuberculosis Elimination 2017-2025 has proposed a vision for TB-Free India with zero deaths, disease and poverty due to tuberculosis and aims to achieve a rapid decline in burden of TB, morbidity and mortality while working towards elimination of TB in India by 2025 integrating four strategic pillars of "Detect – Treat – Prevent – Build" (DTPB)(10).

Treatment of TBM consists of rapid institution of decongestive and anti-inflammatory measures like mannitol, glycerol, acetazolamide and steroids along with Anti Tuberculosis Treatment (ATT). For drug sensitive tuberculosis, administer daily fixed dose combinations (FDC) of first-line anti-tuberculosis drugs in appropriate weight bands along with pyridoxine for

all forms of TB. In all ages, four drugs FDC are administered in the intensive phase and three drug FDCs in the continuation phase as per National Tuberculosis Elimination Program (NTEP) (9). The continuation phase is to be extended for a total of 10 months (Table 1).

A Cochrane review on corticosteroids for managing TBM concluded that corticosteroids reduced mortality in both adults and children by 25 per cent at two months to two years after its initiation. It is likely that most patients are helped and some are harmed by steroids (8).

In conclusion, it is extremely important to identify CNS tuberculosis in early stage to have intact neurological outcome and avoid devastating permanent sequalae and mortality.

References

1. Ministry of Health with Family Welfare. TB India Report 2022 available from TBAnnaulReport2022.pdf (tbcindia.gov.in). Accessed on 22nd August 2022
2. Yaramis¸ A, Gurkan F, Elevli M et al. Central nervous system tuberculosis in children: a review of 214 cases. Pediatrics 1998; 105: e49–e53.
3. Aulakh R, Chopra S. Pediatric Tubercular Meningitis: A Review. Journal of Pediatric Neurosciences , volume 13, Issue 4 ; October-December 2018
4. Israni AV, Dave DA, Mandal A, et al. Tubercular meningitis in children: Clinical, pathological, and radiological profile and factors associated with mortality. J Neurosci Rural Pract 2016;7:400-4.
5. Nataprawira HM, Gafar F, Nelly A. Risan et al. Treatment Outcomes of Childhood Tuberculous Meningitis in a Real-World Retrospective Cohort, Bandung, Indonesia. Emerging Infectious Diseases, www.cdc.gov/eid ,Vol. 28, No. 3, March 2022
6. Kunju PAM, James J. Central Nervous System Tuberculosis in Children. PediatrInf Dis 2019;1(1):23-29.
7. Fatema K, Rahman MM, Shaheen Akter S, et al. Tubercular Meningitis in Children: An Update. Bangladesh J Child Health 2014; Vol 38 (2) : 86-93
8. Daniel BD, Grace GA, Natrajan M. Tuberculous meningitis in children: Clinical management & outcome. Indian J Med Res 150, August 2019, pp 117-130
9. Singh V, Parakh A. What Is New in the Management of Childhood Tuberculosis in 2020?: Indian Pediatrics, Volume 57, 1172-1176 December 15, 2020
10. Ministry of Health with Family Welfare. National Strategic Plan for Tuberculosis: 2017-25. Revised National Tuberculosis Control Programme. March 2017. Accessed June 06, 2022. Available from: https://tbcindia. gov.in