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Research Article

Current Trends in Diagnosis and Management of Pediatric Tuberculosis: A Clinician's Perspective

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Abstract: Tuberculosis in the pediatric age group remains one of the most important diseases causing significant morbidity and mortality. In children, extrapulmonary tuberculosis and disseminated tuberculosis are more common. Because most childhood tuberculosis is oligobacteria, these cases are often difficult to diagnose. Although the Mantoux test is easy to perform, it only detects Mycobacterium tuberculosis infection and does not always indicate active disease. Gastric aspiration is more suitable for microscopic examination than induced sputum in children who cannot spit out multiple sputum and must swallow. Direct microscopy using special stains, such as Zeihl Nielsen stain, is highly specific for diagnosing cases of tuberculosis, especially sputum-positive pulmonary tuberculosis, but is more operator-dependent and less sensitive than modern diagnostic tests such as GeneXpert. GeneXpert can also identify rifampicin-resistant Mycobacterium tuberculosis so that appropriate treatment decisions can be made.
Keywords: tuberculosis; children; pulmonary; gastric aspirate

Introduction

Tuberculosis is still the most frequent infectious cause of death in world even though hundred years have been elapsed since the disease and six decade since the anti tubercular drugs were diagnosed. India accounts 25% of incidence cases of Tuberculosis in the world. About 40% populations in India are infected with tuberculosis. It has been ensured 10 % of actual total TB case load in India among the children[1]. Childhood Tuberculosis is indicated as the recent transmission and thus self as a sentinel event. Children are not only at higher risk of developing the disease but also are more likely to develop the severe form of the disease. Childhood Tuberculosis is indicated as the recent transmission and thus self as a sentinel event. Children are not only at higher risk of developing the disease but also are more likely to develop the severe form of the disease[2].

Burden of pediatric tuberculosis

Around 1/3 of world population are infected with tuberculosis. About 9.4 million new cases & 1.8 million deaths per year worldwide are due to tuberculosis. About 15-20% global TB disease burden is found in children < 15 yrs. This indicates continued transmission in settings with poor epidemic control. About 95% cases in <12yr age are smear negative. Around 80% of tuberculosis affected population resides in 22 highest burden countries including India[3]. Increasing numbers of tuberculosis cases are still being detected in developing world due to HIV epidemic (> 34% co- infected with tuberculosis), poverty, overcrowding, and malnutrition. Travel, MDR-TB and XDR-TB /Incomplete treatments and breakdown of TB control programs[3].

Pediatric tuberculosis: What is different?

It indicates recent transmission from infected adult and is a measure of TB control in community, rarely transmit TB. It has higher risk & more rapid progression to active disease. About 95% of children who develop TB, usually it occurs within 12 months of primary infection. It is a reflection of immature immune system: especially innate immunity (macrophages), dendritic cells and CD 4 positive T-cell[4]. Extrapulomnary tuberculosis like

CNS tuberculosis is relatively more common. Similarly disseminated tuberculosis is also more common in children and also the mortality and morbidity rate. Diagnosis of tuberculosis in children also has several unique challenges, as most of these infections are paucibacillary[4].

Diagnosis of tuberculosis

Diagnosis of tuberculosis in children is often difficult and delay in view of low sensitive microscopy, slow process of culture, non specific shadow in chest radiography and imprecise tuberculosis skin testing. The diagnosis of TB is based on identification of expanded for AFB in sputum. This is often not possible in children[5]. Hence, gastric lavage /aspirate are used for establishing diagnosis of tuberculosis. Induced sputum with hypertonic saline can be used as an alternative in gastric lavage in older children. Induced sputum is less invasive and more comfortable for the child as well as parents. However, use of AFB positivity and culture positivity is better with gastric aspirate[5].

Recent Principles of Diagnosis

- All efforts should be made to demonstrate microbiological evidence (AFB smear, Mycobacterium tuberculosis culture or Cartridge based nucleic acid amplification technique (CBNAAT) in the diagnosis of pediatric TB. In cases where sputum is not available for examination or sputum microscopy fails to demonstrate AFB, alternative specimens(Gastric lavage, Induced sputum, bronch-alveolar lavage) should be collected, depending upon the feasibility, under the supervision of a pediatrician[6]
- A positive tuberculin skin test/Mantoux positive is defined as10 mm or more induration. The optimal strength of tuberculin 2 TU(RT 23 or equivalent) to be used for diagnosis in children.
- There is no role for serology (IgM,IgG,IgA antibodies against MTB antigens), Various in-house or non-validated commercial PCR tests and BCG test. There is no role of IGRAs in clinical practice for the diagnosis of TB.
- Unlike various in house PCR tests, Catridge based Nucleic Acid Amplification techniques (CBNAAT)) is the recommended test for Mycobacterium tuberculosis. There are three main advantages of CBNAAT: Firstly, rapid availability of result indicates presence or absence of tuberculosis within 2 hours; Secondly, it indicates presence or absence of resistance to rifampicin; Thirdly ,being catridge based, it has an inherent system of quality control, obviating risk of cross contamination. Presently its use is recommended in all children with pulmonary and/or extra pulmonary tuberculosis. For respiratory (Sputum,gastric lavage,induced sputum) and for non respiratory(Lymph node aspirates,CSF) specimens are used. In patients with associated HIV suspected MDR TB, suspected TB meningitis or with severe illness,CBNAAT is strongly recommended as the preferred initial test instead of the conventional smear and culture. A negative result does not definitively rule out tuberculosis. Due to lack of evidence, these recommendation do not apply to its use in stool, urine or blood[6].
- Loss of weight was defined as a loss of more than 5% of the highest weight recorded in the past three months. Children cannot usually bring out sputum and gastric aspirates are often negative with TB. Still, it is important to obtain early morning gastric aspirates, or sputum or pleural fluid for ZN (Ziehl-Neelsen) staining and examination for acid fast bacilli and for culture. Radiological investigations may be useful, if tuberculosis is suspected. In addition, a positive skin test is a useful pointer. Mantoux test can however, be negative in military, severe malnutrition, or recent measles[7].

Procedure for collection of Gastric Aspirate and Induced Sputum

Gastric aspiration/lavage

Gastric lavage should be collected in the morning preferably in an admitted patient after overnight fasting before the child wakes up. A nasogastric

tube should be gently placed at night before the child sleeps. If this is not feasible gastric lavage can also be collected, if the child is brought to the health facility in the morning after overnight fasting. The length of the tube to be inserted is equal to the distance measured from tip of the nose to tragus plus from tragus to the xiphisternum. Tube can be advanced for an inch extra so as to reach the stomach. The position of the tube should be checked by pushing 5 ml air through the nasogastric tube and hearing for a gush of air below the xiphisternum[8].

Sample can be aspirated in the morning, while the child is still asleep, by connecting 10 ml syringe to the nasogastric (NG) tube. Sample should be collected over two consecutive days. If gastric aspirate is less than 10 ml the position of the Ryles tube should be rechecked and an extra 10 ml, the patient should be rotated to the left lateral position and again aspiration tried through the nasogastric tube. If still no aspirate, an extra 10ml normal saline should be introduced through the same NG tube and aspiration repeated. If still no aspirate, the patient should be turned to right lateral position and gentle suction done again through the nasogastric tube. If Gastric Aspirate is still less 10 ml, additional normal saline of 10 ml should be introduced via nasogastric tube until a minimum of 10 ml is aspirated. After procedure the nasogastric tube should be gently removed by closing its cap or pinching the tube[8].

Induced sputum:

Sputum induction should be undertaken after 2-3 hours fasting on two consecutive days. Baseline values of respiratory rate, pulse rate, chest rate, chest retractions, wheeze, oxygen saturation should be taken prior to the nebulisation. These parameters should be monitored before and during the procedure and for a duration of 30 minutes after taking the sample. Child should be first nebulised with asthalin 0.2mg/kg in 5ml normal saline. This step is to prevent respiratory distress in children who are predisposed to it after being nebulized with hypertonic saline. Then child should be nebulized with 5ml of hypertonic (3%) sterile saline via a jet nebulizer attached to oxygen at a flow rate of 7-10 L/Min for 10 to 15 minutes[8].

Newer Diagnostic tests

Xpert MTB/RIF

This is the first automated molecular test for TB (CB NAAT assay-catridge based nucleic acid amplification assay), which has excellent performance in smear positive and negative patients. It has high accuracy for determination Rifampicin resistance. It is a simple to use system and detects M tuberculosis directly from sputum in <2 hrs. Currently it is recommended for diagnosis of tuberculosis in national program[9].

Other diagnostic tests

IGRAs (interferon-γ release assays)

T-cell-based IGRAs for latent TB infection have excellent specificity (higher than the TST), unaffected by previous BCG vaccination. IGRAs cannot distinguish between latent TB infection & active TB, &have no role for active TB diagnosis in adults. IGRAs correlate well with markers of TB exposure in low-incidence countries. IGRA sensitivity varies across populations & tends to be lower in high-endemic countries & in HIV-infected individuals. Brand names available are T-Spot.TB (IGRA) and QuantiFERON-TB Gold. Result of this blood test is available in 24 hours. Currently in India it is not recommended[10].

Adenosine deaminase (ADA) level can be used for diagnosing for TB pleuritis, pericarditis, peritonitis by measurement of ADA concentrations in pleural, pericardial, ascitic fluid. Automated liquid cultures for pulmonary TB like mycobacterium growth indicator tube (MGIT) are more sensitive than are solid cultures and time to detection is more rapid than for solid cultures. It takes around 3-6 weeks for final result and uses fluorescent material for easy detection. Diagnosis of latent TB can be done by tuberculin skin testing (TST)[11]. It is also called mantoux ttest, based on delayed cellular hypersensitivity to tuberculin antigen (5-10 unit), adminbistered on volar aspect of forearm and results are read after 48-72 hours. Induration more than 10 mm is considered positive, but it only indicates infection, not sympotomatic diseaseDiagnosis of drug Resistant TB is usually by Phage amplification assays for rapid detection of rifampicin resistance or Line-probe assays[11].

Radiological investigations and fine needle aspiration cytology/truecut biopsy involving the

affected part often helps in solving the dilemma of establishing the definitive etiology.

Treatment of Pediatric Tuberculosis

DOTS is the recommended strategy for treatment of TB and all pediatric TB patients should be registered under RNTCP.At present it has been decided to introduce daily reginmen for treatment of drug sensitive Tuberculosis under revised National Tuberculosis Programme. The various antitubercular drugs used and the treatment regimen followed have been described in table 1, 2, 3 and 4. Currently national program favors daily regimen of antitubercular drugs in children as compared to intermittent regimen. First line antitubercular drugs are Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin. Duration of antitubercular therapy differs from 6 months in pulmonary tuberculosis to at least 9 to 12 months in neurotuberculosis. Index TB guidelines are followed for cases of extrapulmonary tuberculosis[12].

Types of TB treatment recommended in India

It is very important that patients receive the correct TB treatment. This usually means that they must receive the correct TB drugs, as surgery is not very often used for TB treatment. The clinician should inquire about any history of previous ATT intake or any possibility of drug resistant tuberculosis in index case or family members, as prevalence of drug resistant TB in India is increasing year by year[13].

History of TB treatment

Patient will be in one of three groups based on their history of TB treatment. These groups are:

a) **New TB patients** - these are TB patients who have never had treatment for TB or they have taken anti TB drugs for less than one month.

b) **Previously treated patients** - these are patients who have received one month or more of anti TB drugs in the past.

Recurrent TB patients are patients who have previously been considered as successfully treated (cured/treatment completed) and they have subsequently been micro biologically confirmed as still having TB. **Treatment after failure** patients are those who have previously been treated for TB and their treatment failed at the end of their most recent course of treatment. **Treatment after lost to follow-up** is a TB patient who has previously received TB treatment for a month or more and they were declared lost to follow up in their most recent course of treatment. They have also subsequently been found to be a microbiologically confirmed TB case. **Other** previously treated patients are patients who have previously been treated but whose outcome after their most recent course of treatment is unknown or undocumented[13].

c) **Transferred in** - is a TB patient who is received for treatment in a TB unit, after being registered for treatment in another TB unit. **A micro biologically confirmed TB case** refers to a patient who is presumed to have TB and who has a biological specimen positive for acid fast bacilli. It is also a patient positive for TB through a quality assured Rapid Diagnostic Molecular test, such as CBNAAT. The groups, or categories, are similar to, but are not exactly the same as the WHO Treatment categories[14].

Treatment for new TB patients

All new TB patients in India should receive an internationally accepted first line treatment regimen (a regimen is the prescribed course of treatment, in this case the TB drugs) for new patients. The initial intensive phase should consist of eight weeks of the drugs Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E). The continuation phase should consist of the three drugs Isoniazid, Rifampicin and Ethambutol given for another sixteen weeks. This is alternatively written as 2HREZ/4HRE. There will be no need for any extension of the continuation phase. The drug dosages should be given according to the body weight of the patient. There are four weight band categories. All patients should receive their daily TB drugs under direct observation (DOTS)[15]. Under DOTS (Directly Observed Therapy Short Term) the patient has to take the TB medication in front of a DOTS agent. The DOTS agent is usually a volunteer from the patient's community, and may be a family member. DOTS does not say which drugs should be taken. DOTS applies when any TB drugs are taken with the patient being observed by a DOTS volunteer[15].

Fixed dose combinations

A fixed dose combination (FDC) is when two or more drugs are combined together in a single pill or tablet. Fixed dose combinations are helpful as they simplify getting TB drugs and the delivery of DOTS. They may also increase adherence. Individually worked out drug dosing should be only used for patients with toxicities or contraindications to one or more parts of the FDC. Fixed dose combinations of four drugs (Isoniazid, Rifampicin, Pyrazinamide and Ethambutol), three drugs (Isoniazid, Rifampicin and Ethambutol) and two drugs (Isoniazid and Rifampicin) should be available[16].

Daily drug treatment

RNTCP in 2017 proposed this daily drug regimen in public sector also, which was prevalent in private sectors for many years beforehand and concluded that under the new daily drug regimen, TB patients will be given fixed dose combinations (FDCs) - three or four drugs in specific dosages in a single pill - on a daily basis. The drugs will also be administered in a more scientific manner, according to the patient's weight[17]. The biggest advantage for the patient under the new regimen will be reduced pill burden, as instead of seven tablets, patients need consume only 2 or 3 tablets, according to their weight band. However, as the drug regimen goes from three times a week to daily, more monitoring of patients may be required, as with the increased doses the patients may have more side effects[18]. The quantity of the drugs to be taken will also depend on the patient's weight. Each patient will receive through the RNTCP a month's supply of drugs. The patients will be supervised taking the drugs using the DOTs strategy. The daily regimen will have to be followed by patients for six to eight months[19].

Nutritional support

Each patient with TB in India is now to receive R500 a month for food. This is because under nutrition is a risk factor for TB in India. There is more about Nutrition & TB and Food & TB[20].

Previously treated patients

Previously streptomycin was given to many previously treated patients and many patients lost their hearing as a result of the side effects of the drug. The treatment provided was to be as set out in the Programmatic Management of Drug Resistant Tuberculosis (PMDT) in India. However, in December 2018 an announcement was made that all previously treated patients should receive a standard six month first line treatment if no resistance was detected to either rifampicin or isoniazid[21]. This brings the TB treatment in line with the WHO treatment advice. It is however very important to ensure that drug susceptibility testing is carried out to ensure that the previously treated patient does not have any drug resistance[21].

WHO treatment regimen for tuberculosis

The World Health Organisation (WHO) changed their advice for the treatment of previously treated patients in 2017. Their advice now is that patients who require retreatment should never be given streptomycin unless it is part of a regimen for drug resistant TB when no other drug is suitable[22].

Patients who require retreatment should always be referred for a rapid molecular test or drug susceptibility testing to determine if they have drug resistance[23]. If the drug susceptibility testing shows that they have no drug resistance, then the six month first line treatment regimen (2HRZE/4HR) can be repeated. If drug resistance is present, then an MDR-TB regimen should be prescribed according to WHO's drug resistant TB guidelines. There are some difficulties when testing for second line drugs is not available, so this should be made available urgently[23].

The TB drugs for RNTCP patients are supplied in an individual patient wise box which contains the entire course of treatment for the patient. In each patient wise box there are two pouches. One is for the intensive phase and the other is for the continuation phase.The patient wise boxes are colour coded. Red boxes are for new patients, sometimes referred to as category 1. Blue boxes are for previously treated patients and are sometimes referred to as category 2. For paediatric TB patients separate patient wise boxes have been developed[24].

The terminology for treatment categories of patients is slightly confusing. The World Health Organization (WHO) has also had treatment categories for patients. In the same way that the use of the term Treatment Categories is no longer

used by the WHO, so the phrase Categories of Treatment is no longer used in India[25].

Monitoring treatment response

The response to therapy in patients with pulmonary TB, both new and retreatment patients should be monitored. This should be done by follow-up sputum microscopy/culture (one specimen) at the time of completion of the intensive phase of treatment and at the end of treatment[25].

Role of Corticosteroids in TB

Corticosteroids reduce morbidity in patients suffering from Central nervous system TB; military disease with alveolar-capillary block; pericarditis and pericardial effusion; endobronchial TB leading to partial or complete airway blockage, severe paradoxical response to drugs; and occasionally peritonitis or massive pleural effusions[26]. All children with TB meningitis should b treated with adjuvant steroids irrespective of disease severity (Prednisolone 2 mg/kg/day,maximum 60 mg/day or Dexamethasone 0.6mg/kg/day for 4 weeks followed by reducing course over 4weeks). Although helpful in certain patients, corticosteroids should not be prescribed injudiciously due to its potential to cause dissemination of TB[27].

Conclusion

All efforts should be made to demonstrate bacteriological evidence for the diagnosis of pediatric TB. Children with TB are classified, categorized, registered and treated with daily short-course chemotherapy, given under direct observation of a treatment provider and the disease status is monitored during the course of treatment. All childhood TB patients should be registered under RNTCP. There will be only two treatment categories-one for treating' new' cases and another for treating 'previously treated 'cases. Despite availability of effective chemotherapy in India, control has not been achieved because of poor therapeutic practices. Of course road ahead will be tough but contribution, involvement and commitment from all concerned in implementing the guidelines will ultimately benefit the children of our country.

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