Diagnostic Yield of Xpert MTB/RIF in Bronchoalveolar Lavage in Children with Probable Pulmonary Tuberculosis

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Objective: To evaluate utility of Xpert MTB/RIF in bronchoalveolar lavage fluid in children with probable pulmonary tuberculosis. **Methods:** Children with probable pulmonary tuberculosis with negative smear and Xpert on induced sputum/gastric aspirate were subjected to bronchoalveolar lavage (BAL) for Xpert assay and mycobacterial liquid culture. Data of children <14 y undergoing bronchoscopy for suspected MDR-TB (*n*=12) were also analyzed. The sensitivity of Xpert in BAL fluid for diagnosis of probable and confirmed pulmonary tuberculosis was calculated with clinico-radiological diagnosis and culture as gold standards, respectively. **Results:** Of 41 enrolled children, 24 (58.5%) had Xpert positive in BAL fluid and 11 (26.8%) had culture confirmed tuberculosis (BAL fluid;10; sputum,1). The sensitivity of Xpert in BAL fluid among probable and culture confirmed tuberculosis cases was 58.5% (24/41) and 81.8% (9/11), respectively. **Conclusion:** Xpert in bronchoalveolar lavage fluid has good sensitivity in both probable and confirmed pulmonary tuberculosis in children.

Keywords: *Bronchoscopy, CBNAAT, Pediatric TB.*

Microbiologic confirmation of childhood tuberculosis is challenging because of low and variable sensitivity of culture and the difficulty in obtaining appropriate samples in children. In addition, turnover time of culture is usually in weeks. Xpert MTB/RIF (*Mycobacterium tuberculosis/Rifampicin*) is a point-of care diagnostic test that can be performed with minimal training and results are available within two hours [1]. Utility of Xpert MTB/RIF assay on respiratory specimens in adults is well established [2]. After endorsement by the World Health Organization [3], several studies have evaluated the utility of Xpert MTB/RIF assay for the diagnosis of pediatric tuberculosis [4-10]. However, data on diagnostic utility of Xpert MTB/RIF assay using bronchoalveolar lavage (BAL) fluid in children are limited [11,12]. We evaluated the utility of Xpert MTB/RIF on BAL samples in children with clinico-radiological suspicion of pulmonary tuberculosis.

METHODS

The study was carried out in the Pediatric Pulmonology Division of All India Institute of Medical Sciences, New Delhi, between January 2015 and October 2016. The study was approved by Institute Ethics Committee. The criteria for probable pulmonary TB were [13]: Any of the clinical symptoms: cough and/or fever >2 weeks, weight loss, lethargy; History of contact with adult TB case or positive Mantoux test; and Chest *X*-ray suggestive of tuberculosis.

A minimum of two respiratory samples (gastric aspirate (GA)/expectorated sputum/induced sputum) were collected in all children with probable pulmonary TB and subjected to Ziehl-Neelsen (ZN) smear, MGIT-960 (Mycobacteria growth indicator tube) culture and Xpert MTB/RIF assay. If ZN smear and Xpert MTB/RIF were negative, bronchoscopy and bronchoalveolar lavage was performed; since MGIT culture takes time, we did not wait for MGIT report to decide regarding bronchoscopy. Children with features of treatment failure (non-resolution or worsening of radio-clinical features at the end of intensive phase of treatment) on category 1 anti-tubercular therapy (ATT) or high probability of multi-drug resistant (MDR) TB also underwent bronchoscopy. Children ≤14 years who underwent bronchoscopy for confirmation of probable pulmonary TB or suspected MDR-TB were the study subjects.

Flexible bronchoscopy was performed under conscious sedation with midazolam and fentanyl, after receiving written informed consent from parents. After inspecting all the bronchial segments, BAL samples were collected from the lung segments showing abnormal

lesions on *X*-ray film or CT scan of chest.

BAL samples were analyzed by smear microscopy, Xpert MTB/RIF (Cepheid, Sunnyvale CA, USA), MGIT-960 (Becton, Dickinson and Co, New Zealand) culture and drug susceptibility testing (DST).

Statistical analysis: Sensitivity for Xpert MTB/RIF assay on BAL fluid for the diagnosis of probable and confirmed pulmonary TB were calculated by considering the clinico-radiological diagnosis and liquid culture, respectively as separate gold standards.

RESULTS

Forty-one children (22 boys) with median (IQR) age of 10 (5.5, 13) years underwent diagnostic bronchoscopy during the study period; none were known to be HIV seropositive (*Table* I). Drug-resistant pulmonary TB was suspected in 12 children; nine of them had treatment failure and three had relapsed after treatment. Two patients had contact with MDR-TB patients.

Xpert MTB/RIF, MGIT culture and smear were positive in 24 (58.5%), 10 (24.4%), and 4 (9.7%) BAL samples, respectively (*Table* I). Eleven (26.8%) were culture confirmed TB (BAL=10, sputum=1). Comparison of Xpert MTB/RIF in BAL fluid with MGIT culture and ZN staining is presented in *Table* II.

Xpert MTB/RIF and MGIT culture in BAL fluid were positive in 58.5% (24/41) and 24.4% (10/41), respectively. The sensitivity and specificity of BAL Xpert MTB/RIF in detecting culture confirmed TB was 81.8% (9/11) and 50% (15/30), respectively; positive- and negative-predictive values were 37.5% (9/24) and 88.2% (15/17), respectively.

Xpert MTB/RIF could identify an additional 15 (36.6%) cases, where all other microbiological investigations were negative.

Among suspected MDR-TB patients, drug resistance

TABLE I Characteristics of Children with Probable Pulmonary Tuberculosis (*N*=41)

Characteristics	Values
History of TB contact	7 (29.3%)
No BCG scar	13 (31.7%)
Positive Mantoux test	24 (58.5%)
BAL sample	
AFB smear positive	4 (9.7%)
Xpert positive	24 (58.5%)
MGIT culture positive	10 (24.5%)
Final diagnosis	
Probable pulmonary TB	41 (100%)
BAL (AFB/Xpert/MGIT) confirmed TB	25 (61%)

Abbreviations: IQR: interquartile range, BAL: bronchoalveolar lavage; AFB: acid fast bacilli; BCG: Bacillus Calmette–Guérin; MGIT: Mycobacteria Growth Indicator Tube; TB: tuberculosis.

was identified in three (27.3%) by BAL MGIT culture and DST. However, rifampicin resistance by Xpert MTB/RIF in BAL fluid was documented in two patients (2/11) (*Table* II). The three confirmed drug resistant patients were started on second line anti-TB drugs. Three additional children were positive with BAL Xpert MTB/RIF over the MGIT culture, though they were rifampicin sensitive. These patients were started on Category II ATT.

DISCUSSION

In this diagnostic study, we observed that Xpert MTB/RIF assay on BAL samples has good sensitivity in both probable (58.5%) and confirmed (81.8%) pulmonary tuberculosis in children. BAL Xpert resulted in additional diagnostic yield and also in the rapid detection of drug resistance in children with probable pulmonary tuberculosis.

TABLE II Comparison of Bronchoalveolar Lavage Xpert in Probable Pulmonary Tuberculosis (*N*=41) and Suspected Drug Resistant Pulmonary Tuberculosis (*N*=12) with Culture and ZN Smear

BAL Xpert	MGIT culture		ZN smear	
	Positive	Negative	Positive	Negative
Probable pulmonary TB (n=41)				
Positive	9 (81.8%)	15 (50%)	4 (100%)	20 (54%)
Negative	2 (18.2%)	15 (50%)	0	17 (46%)
Suspected drug resistant pulmonary TB (n=12)				
Positive	2 (66.7%)	3 (33.3%)	3 (100%)	2 (22.2%)
Negative	1 (33.3%)	6 (66.7%)	0	7 (77.8%)

Abbreviations: BAL: bronchoalveolar lavage; TB: tuberculosis; ZN: Ziehl Neelsen; MGIT: Mycobacteria Growth Indicator Tube.

WHAT THIS STUDY ADDS?

• Xpert MTB/RIF assay of bronchoalveolar (BAL) fluid may be used for rapid diagnosis of smear negative pulmonary tuberculosis and drug resistance in children and may aid in taking early treatment decisions.

The present study is limited by small sample size. We could not estimate specificity for BAL Xpert assay in probable pulmonary TB as the control group of children without tuberculosis were not enrolled.

In our study, sensitivity of BAL Xpert MTB/RIF was higher than culture among sputum/GA smear negative probable pulmonary TB patients. Similarly, Walters, *et al.* [11] found higher sensitivity of BAL Xpert MTB/RIF in children with suspected complicated pulmonary TB (78%) as compared to culture (64%) [11]. A study done in Chinese children [12] also showed higher sensitivity of BAL Xpert MTB/RIF (53%) as compared to culture (28.9%). In our study, we found sensitivity of 81.8% for Xpert MTB/RIF on BAL samples in culture-confirmed cases, which is similar to that reported in adults earlier (78%-92.3%) [11,14-15].

One of the strengths of Xpert MTB/RIF assay is to detect rifampicin resistance within same day, which can facilitate early diagnosis and treatment of MDR TB. In the present study, BAL Xpert MTB/RIF successfully identified two of the three rifampicin resistant cases. In case of suspected drug resistant TB, MGIT culture may still be the preferred test and Xpert assay may be used as add-on test for rapid detection of these cases.

We conclude that BAL Xpert MTB/RIF assay may aid in clinical management of probable pulmonary tuberculosis in children by improving case detection and enabling the treating physician to take early decisions.

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