



Evaluation of Gene Xpert Ultra Against Conventional Technique for the Diagnosis of Extrapulmonary Tuberculosis in Children in A Tertiary Care Center

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Abstract: Background: EPTB receives less attention than PTB because of its low infection potential. Clinically EPTB is still under recognized and diagnosis are often delayed due to its paucibacillary nature and atypical presentation. Proper diagnosis needs isolation of organism, that is always not possible by doing AFB staining, culture of different body fluid, biopsy only. Gene Xpert MTB/RIF Ultra (Xpert Ultra) was evolved to prevail over this limitation. **Materials & Methods:** In this prospective, single center, cross-sectional, diagnostic performance study which was conducted at the department of Paediatrics in Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh over 1 year period. Different body fluid (CSF, ascetic fluid, pleural fluid, pus etc) for AFB staining, micobacterialculture, Xpert MTB/RIF Ultra, biopsy for histopathology of children presenting with presumptive extra pulmonary tuberculosis were tested with Adenosine deaminase (ADA) & other baseline investigations. Total 80 children having the clinical features of extra pulmonary tuberculosis were enrolled and evaluated. Diagnostic performance (sensitivity, specificity, positive & negative predictive value) of Gene Xpert MTB/RIF Ultra were analyzed. **Results:** From January, 2021 to december, 2021 total 80 patients were evaluated. Among them, 17.5% were diagnosed as TBM & 11.3% were TB lymphadenitis, 6.3% were abdominal TB, 3.8% were pleural TB, 1.25% were spinal TB. AFB staining positive in 4.8% (3 of 62), culture growth positive in 8.06% (5 of 62) & Gene Xpert Ultra positive in 37.97% (30 of 79) cases. Against the mycobacterial culture results and AFB staining, Xpert Ultra had sensitivity of 100.0% (69.2 – 100.0; p 0.001) &100.0% (26.2 to 87.8; p 0.01), respectively. Xpert Ultra had specificity of 73.7% and 71.2% respectively. **Conclusion:** Xpert Ultra detected extra pulmonary tuberculosis with higher sensitivity than culture and AFB staining in paediatric population.

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Article at a glance:

Study Purpose: To evaluate the accuracy of Gene Xpert Ultra in diagnosing pediatric extrapulmonary tuberculosis (EPTB) compared to AFB staining and culture.

Key findings: Gene Xpert Ultra had 100% sensitivity, significantly outperforming AFB staining (60%) and culture.

Newer findings: Gene Xpert Ultra offers a rapid, highly sensitive alternative for diagnosing pediatric EPTB, though its specificity is lower.

Abbreviations: EPTB – Extrapulmonary Tuberculosis, AFB – Acid-Fast Bacilli, Xpert Ultra – Gene Xpert MTB/RIF Ultra, TBM – Tuberculous Meningitis, TB – Tuberculosis, ADA – Adenosine Deaminase, CSF – Cerebrospinal Fluid, PCR – Polymerase Chain Reaction



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INTRODUCTION

Tuberculosis is the leading cause of death from a single infectious agent. About 90% of new cases are

in 30 high TB burden countries. In the year 2020, TB incidence rate was 221/1,00,000 population in Bangladesh.

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Regarding child TB, it is 43,320 (12%), but the detected cases were only 4.2% (12,350). The SDGs & the END TB strategy settle a target for percentage reduction of TB incidence & death rate by the year 2030 & 2035, respectively (National guideline of TB 2016)¹. There are 0.8 million patients diagnosed with extrapulmonary tuberculosis all over the world, with the most dangerous form being tuberculous meningitis.² Tuberculous meningitis is the most devastating manifestations of TB & early treatment initiation is critical to optimizing outcomes.³

Childhood Tuberculosis constitutes approximately 10-20% of all TB cases in this region, causing almost 8-20% of TB-related deaths. Twenty five percent of the pediatric tubercular cases are extrapulmonary, with tubercular meningitis being the most common cause of death because of TB.⁴ EPTB accounts for about 30% of TB in children, as seen in high burden countries. Extrapulmonary tuberculosis receives less attention than pulmonary tuberculosis because of its low infectious potential⁵. Many patients are diagnosed late because initial signs are nonspecific, rapid & sensitive diagnostic tests are lacking.⁵

Conventional laboratory techniques like direct microscopy for the diagnosis of tuberculosis are far from being sensitive.⁶ ZN smear technique requires a bacillary load of 10^5 /ml to show positivity, therefore making it an unreliable technique in the diagnosis of extrapulmonary tuberculosis⁷. However, culture method, considered as Gold-standard for detection and to know the drug-sensitivity in TB is time consuming and requires strict biosafety infrastructure and trained laboratory staff.⁷ The cheapest test, AFB staining require expert microscopist. Body fluid culture takes several weeks & cannot guide initial treatment decisions.⁸ The purpose of this study was to see the role of Gene Xpert Ultra for detection of EPTB as compared with AFB staining and culture.

OBJECTIVES

To evaluate Gene Xpert ultra for the diagnosis of extra pulmonary tuberculosis in children as compared to conventional technique.

METHODS

Study design: Cross sectional study.

Place of study: Department of Pediatrics, Dhaka Medical College Hospital, Dhaka.

Study Period: January 2021 to December 2021.

Study population: Children age 1 month to 12 years, admitted with presumptive extrapulmonary tuberculosis in department of Paediatrics, DMCH, Dhaka (according to operational definition).

Inclusion criteria

Age 3 month to 12 years.

Clinical manifestation of extrapulmonary tuberculosis.

Exclusion criteria

Patient with pulmonary tuberculosis.

Patient who already have started anti-TB treatment

RESULTS

Table 1: Demographic profile of the cases (n=80)

Variables	Frequency	Percentage (%)
Age group		
3 months to <5 yrs	37	46.3
5 yrs to 12 yrs	43	53.8
Mean±SD	5.34±2.83	
Range	3 months – 12.0 years	
Gender		
Male	48	60.0
Female	32	40.0
Male: Female ratio	1.5:1	

Results were expressed in Mean±SD, range, frequency and percentage.

Table 2: Presentation of Extrapulmonary Tuberculosis (n=32)

Variable	No of patients(n)	Percentage (%)
TB meningitis	14	17.5
TB lymphadenitis	9	11.3
Abdominal TB	5	6.3
Pleural TB	3	3.8
Spine TB	1	1.25

Values of qualitative data were presented as number (percentage).

Table 3: Distribution of the cases according to positive findings in diagnostic investigations (n=80)

Investigations	No of cases	Positive findings	Percentage (%)
Gene Xpert Ultra	79	30	38.0
Culture	62	5	8.1
AFB staining	62	3	4.8
LN Biopsy	10	5	50.0
MRI of brain	10	4	40.0
X-ray Spine	1	1	100.0

Values of qualitative data were presented as number (percentage)

Table 4: Validation of Xpert Ultra using culture, AFB staining and LN biopsy tests as a reference standard.95% confidence intervals for sensitivity, specificity and accuracy

Sample material	Sensitivity	Specificity	PPV	NPV	Accuracy
	% (95% CI) TP/(TP+FN)	% (95% CI) TN/(TN+FP)	% (95% CI) TP/(TP+FP)	% (95% CI) TN/(TN+FN)	% (95% CI) (TP+TN)/ (TP+FP+FN+FP)
AFB staining	100(29-100) 3/3	71(58-82) 42/59	15(10-21) 3/20	100 42/42	72 (60-83) 45/62
Culture	100 (47-100) 5/5	73(60-84) 42/57	25(18-34) 5/20	100 42/42	76(63-86) 47/62
LN Biopsy	100(49-100) 5/5	20(1-76) 1/5	56(19-81) 59	100 1/1	60(26-88) 6/62

DISCUSSION

Total 80 children having the clinical features of extra pulmonary tuberculosis were enrolled and evaluated. Diagnostic performance (sensitivity, specificity, positive & negative predictive value) of Gene Xpert MTB/RIF Ultra were analyzed. Among them, 17.5% were diagnosed as TBM & 11.3% were TB lymphadenitis, 6.3% were abdominal TB, 3.8% were pleural TB, 1.25% were spinal TB. AFB staining positive in 4.8% (3 of 62), culture growth positive in 8.06% (5 of 62) & Gene Xpert Ultra positive in 37.97% (30 of 79) cases. Against the mycobacterial culture results and AFB staining, Xpert Ultra had sensitivity of 100.0% (69.2 – 100.0; p 0.001) & 100.0% (26.2 to 87.8; p 0.01), respectively. Xpert Ultra had specificity of 73.7% and 71.2% respectively. The strength of this study was prompt and accurate diagnosis of EPTB cases by Gene Xpert ultra with the help of well-equipped ICDDR, B laboratory. Ultra showed 100% sensitivity in comparison to AFB staining, culture and LN biopsy means there was no chance of false negativity. Ultra is a useful add-on test that can contribute to a rapid diagnosis of EPTB in our setting. The weakness of this study was small number of bacteriologically confirmed TB cases may be due to paucibacillary nature of EPTB cases, less trained personel, contamination of culture, available use of antibiotic. Xpert ultra had lower specificity (71%, 73%, 20%) in comparison to AFB staining, culture and LN biopsy that means there may be chance of false positive results. The inability of Ultra to separate viable from non-viable bacilli and the lack of information about drug resistance for “trace” positive samples, limits its use in some clinical cases, especially in patients previously treated for TB.

Here EPTB cases were 40% (32 of 80). Rafaela Baroni *et al.* (2020) found EPTB cases 31%. Out of 40% TB meningitis cases were 17.5%, TB lymphadenitis 11.3%, abdominal TB 6.3%, pleural TB 3.8%, spine TB 1.3%. Pandey D *et al.* (2019) found EPTB cases 34.6% in which TB meningitis 18%, TB lymphadenitis 8%, pleural TB 8.7%. Regarding sensitivity, Xpert Ultra had 100% sensitivity, which was significantly higher than AFB staining (60%) and culture of different sample in this study. Chin *et al.* (2019) demonstrated that sensitivity of Xpert Ultra was 70%⁹. A study in

China, Shao *et al.* (2020) found that Xpert Ultra had 93.3% sensitivity, similar to this study¹⁰. Xpert Ultra had reduced specificity of 71.2% and 73.7% than AFB microscopy and culture. Shao *et al.* (2020) demonstrated Xpert Ultra had 100% specificity, dissimilar with this study¹¹. Another study showed significantly higher specificities for Xpert Ultra (93.9%)¹⁰⁻¹⁵. The findings regarding specificity of Gene Xpert Ultra is reduced in this study. This may be due to a significant number (23.3%, 7 of 30) of positive Xpert Ultra results were in the trace category.

CONCLUSION

According to the present study results, Gene Xpert MTB/RIF Ultra was found significantly sensitive than culture and AFB microscopy for diagnosis of extra pulmonary tuberculosis in children.

Limitations of the study

It was a single center study. Sample size was small. Single reference laboratory was used. Inappropriate sample collection due to pandemic Covid 19 situations.

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