

Diagnosis of Pulmonary Tuberculosis by Xpert MTB/RIF Assay Using Gastric Aspirate in Children with Pneumonic Consolidation

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Abstract

Background: In Bangladesh, there is increased evidence of TB-associated pneumonia in children are currently missed or diagnosed too late resulting in deterioration of condition. The objective of this study was to detect the frequency of pulmonary TB in children presented with pneumonic consolidation by Xpert MTB/RIF assay using gastric aspirate.

Materials & Methods: This was a prospective observational study. Admitted children from 6 months to 14 years old from January to December 2020 with clinical features consistent with pneumonia and radiographically confirmed consolidations were enrolled in this study. MT and Xpert MTB/RIF assay using gastric aspirates were done in all cases. Data regarding frequency of TB, clinical features and lab findings of enrolled patients were collected and analyzed.

Results: Total 7/60 (11.67%) enrolled patients, were confirmed as Pulmonary Tuberculosis by Gene Xpert using gastric aspirates. The most common clinical signs were fever and cough in all (100%) patients. Others had chest pain 23(38.33%), breathing difficulty 21(35%), vomiting 17(28.33%). Younger children less than 5 years ($P=.045$), contact with TB patient ($P=.001$), long duration of fever ($P=.001$), presence of severe acute malnutrition ($P=.001$) high ESR ($P=.009$), positive MT ($P=.017$) were associated with positive rate of Xpert MTB/RIF assay in children.

Conclusions: Xpert MTB/RIF assay can assist in fast diagnosing childhood pulmonary TB especially in patients with fever more than one week, malnutrition and having contact with TB patient.

Keywords: Tuberculosis (TB), Consolidation, Gene X-pert, Gastric Aspirates.

DOI: <https://doi.org/10.3329/bjch.v46i2.72113>

Introduction:

Tuberculosis is a chronic infection caused by Mycobacterium tuberculosis. It is one of the most common infectious causes of death in the world.¹ The World Health Organization launched the End TB Strategy in 2015. The WHO estimates that 10 million people developed TB in 2018, among them 90% were adults and 10% were children (aged <15 years). TB caused an estimated 1.2 million deaths among HIV-

negative people and of them 14% were children.² Tuberculosis remains a major public health problem in Bangladesh. In Bangladesh where tuberculosis notification rate is 4% grossly underestimates the true extent of the problem where the global estimated TB patient is 11%.²

Pulmonary TB is a chronic disease, but it can present as an acute pneumonia. Acute tuberculous pneumonia is similar to typical bacterial pneumonia.³ Acute Tuberculous Pneumonia generally may present as community-acquired pneumonia, but the pathogen is Mycobacterium tuberculosis rather than non-tuberculous bacteria or viruses.⁴ About 7.5% of paediatric pneumonia was associated with confirmed Mycobacterium tuberculosis by culture in TB-endemic areas, which underestimate the true burden due to difficulties of obtaining microbiologic confirmation in

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Received: 05/08/2021

Accepted: 06/05/2022

children.⁵ Tuberculosis, is a recognized but under-diagnosed, cause of pneumonia, especially in TB-endemic areas. The incidence of Pulmonary Tuberculosis in children admitted with severe pneumonia is high. About one in five case of severe pneumonia in children also having pulmonary TB.⁶ An acute presentation was common in TB Pneumonia but case-fatality rate for pneumonia associated with tuberculosis ranged from 4% to 21%.⁷ Tuberculosis disease was found between 1% and 23% of pneumonia cases.⁸ So, Acute Tuberculous Pneumonia can be easily confused with non-tuberculous community-acquired pneumonia, resulting in deterioration of Tuberculous Pneumonia due to delayed treatment.⁵ Many patients of Tuberculous Pneumonia presented with unilateral pneumonic consolidation.³ WHO declared Xpert MTB/RIF as the initial test for the diagnosis of TB in children, based on sensitivity and specificity of Xpert MTB/RIF performed on gastric lavages of 66% (95% confidence interval 51-81) and 98% (95% confidence interval 96-99), respectively, when compared with culture.^{9,10} Sensitivity of Xpert was 69.6% (95% confidence interval [CI]: 47.1-86.8) among children with Confirmed TB.¹¹ In comparison to sputum culture positive results, the sensitivity of Xpert assay to detect TB pneumonia was 94.5%.¹² Another published results of a multi-centers study in Tanzania, from 215 children, 28(13%) had culture confirmed TB and sensitivity of Gene Xpert was higher (54%).¹³ So, Mycobacterium tuberculosis is an important cause of pneumonia in children, but there are surprisingly few data about this disease diagnosis and burden.¹⁴

Rapid case detection of TB will facilitate prompt treatment and better outcomes. Most of the PTB in diagnosed by smear, culture or molecular tests which are done on expectorated sputum.¹⁵ Detection of Mycobacterium tuberculosis in children is often difficult because they are frequently unable to expectorate sputum or expectorate sputum in the low volume or quality for testing.¹⁵ Mycobacterium Tuberculosis culture needs 3-4 weeks and it requires viable bacterium to detect.¹⁶ On the other hand, Xpert MTB/RIF assay is an automatic molecular test based on semi nested real-time PCR and molecular Beacon technology targeting the *rpoB* gene. It can detect MTB and Rifampicin resistance within few hours.¹⁷ So far, only several studies about Xpert MTB/RIF assay focused on the application of Xpert MTB/RIF in children.¹⁸ So, this study was conducted to determine

the frequency of pulmonary tuberculosis among child presented with consolidation by Xpert MTB/RIF assay using gastric aspirates, their clinical characteristics and factors associated with positive rate of gene Xpert.

Materials and Methods:

A hospital-based prospective observational study was undertaken in the department of paediatrics, Dr. M R Khan Shishu Hospital & Institute of Child Health, Mirpur-2, Dhaka from January 2020 to December 2020. A total of 60 children with respiratory symptoms (cough and/or respiratory distress) and radiological consolidation were enrolled in this study. Based on radiological findings, lobar or segmental consolidation involving any lobe was included in our study. But those with alveolar infiltrate, interstitial infiltrate, pneumatocele, and pneumothorax were not included in our study. Children who had pneumonic consolidation as a part of multi system sepsis, pre-existing chronic illness or co-morbidity, congenital anomalies, congenital heart disease and children whose parents/attending guardians did not give consent were excluded from this study.

Chest radiograph on admission were reported by radiologist. The same clinician visited the patients & recorded information about particulars of the patient, socio-demographic status (age, sex, socioeconomic condition, and immunization history), sign symptoms after taking informed written consent from parents. Anthropometry included weight, height/ length of the enrolled patients were recorded and plotted in CDC (Centers of Disease Control and Prevention) Growth Chart. Weight was taken by Standard Weighing Scale, Supine length was measured by infantometer and Height was measured by stadiometer and Investigations included complete blood count, a tuberculin skin test (TST) and Xpert MTB/rif assay.

A standard procedure of TST was followed and induration was measured at 72 hours. For taking gastric aspirates, patients were instructed to keep nothing per oral for 4 hours prior to conduct the procedure, introduce and fix a sterile nasogastric tube, aspirated gastric contents, collected the specimen in a sterile container & sent for Xpert MTB/RIF assay immediately to the National Tuberculosis Reference Laboratory (NTRL), Mohakhali, Dhaka for processing. All Data were presented in tabulated form. Statistical analysis was performed by chi-square test by using SPSS version 23. The study was approved by the

Ethical Review Committee of Dr. M R Khan Shishu Hospital and ICH. Written informed consent was obtained from parents or caregiver of all the participating children.

Definitions

Lobar Pneumonia: Localized infection of terminal air space causing uniform consolidation of all or part of a lobe retain normal volume and often show air bronchogram.

Positive MT: Transverse diameter of induration >5 mm irrespective of BCG status.

Severe malnutrition: Severe wasting (Z score for weight for height <-3 of the WHO median) for children up to 5 years. For more than 5 years, BMI (Body mass index) was calculated by weight (Kg)/Height (m²) and plotted in BMI for age growth charts (Z score for BMI for age <-3).

RESULTS:

Among the study population, majority of cases 39 (65%) were less than 5 years with an age range from 6 months to 12 years. Male were predominant 40(66.67%) and 20(33.33%) were female. Eight (13.33%) had severe acute malnutrition, 10 (16.67%) patients had a reported history of TB contact and 6(10%) had H/O measles in last 3 months. (Table-1)

Table -I

Characteristics of enrolled children with Pneumonic consolidation (total case n=60)

Characteristics	Frequency (%)
Gender	
Male	40(66.67%)
Female	20(33.33%)
Age	
<5 years	39(65%)
>5 years	21(35%)
Socioeconomic Condition	
Poor	19(31.67%)
Middle/Rich	41(68.33%)
History of TB contact	
Present	10(16.67%)
Absent	50(83.33%)
History of Measles	
Present	6(10%)
Absent	54(90%)
Severe malnutrition	
Present	8(13.33%)
Absent	52(86.67%)

The clinical characteristics of enrolled patients were shown in Figure-1. In this study, most common clinical features were fever and cough and were present in all (100%) cases, followed by breathing difficulty 21 (35%), vomiting 17 (28.33%), dehydration 7 (11.67%), chest pain 23 (38.33%), abdominal pain 14 (23.33%), and BCG mark...

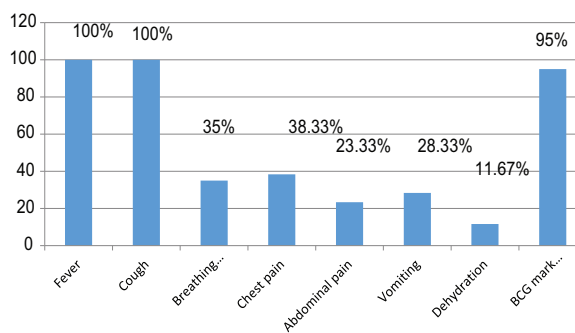


Fig.-1: *Various signs and symptoms of enrolled children presented with Pneumonic consolidation (total case n=60) Tuberculosis*

Among the total 60 enrolled patients, 7 (11.67%) were confirmed to be Pulmonary Tuberculosis by Gene Xpert using gastric aspirates. (Figure-2)

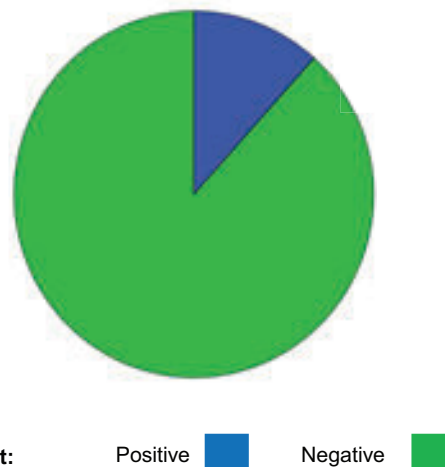


Fig.-2: *Frequency of Pulmonary TB among children with Pneumonic Consolidation*

Table-II showed some factors associated with positive rate of X-pert MTB/RIF assay in children which revealed significant association of younger children less than 5 years, contact with TB patient, long duration of fever, presence of severe acute malnutrition as well as lymphocytosis, high ESR, positive MT.

Table -II

Factors associated with positive rate of Xpert MTB/RIF assay in children with pneumonic consolidation

Factors	Gene Expert	Gene Expert	p value
	Positive (n=7)	Negative (n=53)	
Age			
<5 years	2	37	0.045
>5 years	5	16	
Gender			
Male	4	36	0.429
Female	3	17	
Socioeconomic status			
Poor	4	15	0.135
Middle/Rich	3	38	
History of TB contact			
Yes	5	5	0.001
No	2	48	
Clinical sign & symptoms			
Duration of fever			
<7days	0	37	0.001
>7 days	7	16	
Severe Acute Malnutrition			
Present	3	5	0.043
Absent	4	48	
BCG Scar			
Present	7	50	0.685
Absent	0	3	
Laboratory Investigations			
Leukocytosis			
Yes	4	37	0.389
No	3	16	
Lymphocytosis			
Yes	3	15	0.043
No	4	48	
ESR			
High	7	25	0.009
Normal	0	28	
MT			
Positive	3	3	0.017
Negative	4	50	

Discussion:

Low (10%-15%) positive rate of the AFB microscopy in pediatric Tuberculosis due to paucibacillary sputum is accompanied by difficulty in detection Pulmonary Tuberculosis¹⁹ Another study found the positive rate of AFB microscopy or MTB culture was only 9.7% in childhood TB.²⁰ But, the sensitivity of Xpert MTB/RIF assay was 53.0%, similar to that reported in the study of Nhu et al. (50%).²¹ Thus the above-mentioned studies have showed that Xpert MTB/RIF assay has a good application in childhood tuberculosis and for children with pneumonic consolidation, Gene Xpert using gastric aspirate can assist in diagnosing Pulmonary Tuberculosis. In our study, 7 (11.67%) was confirmed to be Pulmonary Tuberculosis by Gene-Xpert using gastric aspirate which was almost similar to a study done in China which showed 9.4%.¹ Our inclusion criteria of consolidative pneumonia may exclude patients with early pneumonias that have not established on initial CXR.²² The MT was negative in some of our children with confirmed TB which was consistent with a study done by Chisti MJ et al.²³ Expectedly H/O contact with TB was more common in children with confirmed TB which was also consistent with our study.²³

In this study children were between 9 months to 14 years old which was consistent with a study done by Qing-Qin Yin et al. which showed age range of 0.3-15.3 years.¹ The positive rate of detecting TB patients in children younger than 5 year old was significantly higher which was also similar to study done by Qing-Qin Yin et al.¹

In our study, it was observed that males (66.67%) outweighed females which was consistent to the study done by Vamsee K et al. where males are 58%.²⁴ BCG mark present in 57(95%) which was consistent with findings by Qing-Qin Yin et al. which showed 83.1%.¹

In our study, All 60(100%) patients were presented with cough and fever which was consistent with a study done by Vamsee K et al. in India.²⁴ A study was done in Canada by Anne et al. showed fever (94.1%) and cough (89.6%) which was not similar to our study.²² Breathing difficulty was present in 21(35%) cases of our study which is different from a study done in India which revealed (100%).²⁴ Vomiting was present in 21(35%) in contrast to a study done in Canada where it was 53.3%.²² In our study, 10(16.6%) patients have H/O contact with TB patient which was

almost similar to a study done by Qing-Qin Yin et al which was 10.6%.¹

We further explored the factors associated with positive Xpert MTB/RIF result in PTB children presented with pneumonic consolidation. Firstly, we found that age <5 years was associated with a positive result of Xpert MTB/RIF assay in children with pulmonary Tuberculosis and a study by Qing-Qin Yin et al. showed similar findings but a study by E. Walters et al. revealed the age >5 years was associated with a positive Xpert MTB/RIF assay.²⁵ This difference may be explained by different severity of the enrolled PTB children or suggested that Xpert MTB/RIF assay can better detect TB patients in younger children less than 3 years old in our setting. Secondly, reported history of TB contact was also associated with a positive Xpert MTB/RIF assay in this study, which is in line with the previous reports by Sekadde MP et al. and Qing Qin Yin et al.^{1,25} Reported history of TB contact increases the likelihood of suffering pulmonary TB in children. Our results showed that the positive rate of Xpert MTB/RIF assay has no association with BCG vaccination which was not similar to a study done in China.¹ Rodrigues et al. also confirmed that BCG vaccination can protect children from severe TB like miliary TB.²⁵ We also found severe acute malnutrition as an important factor which was consistent to a study done by Chisti JM et al.²³ TB was common in severely malnourished Bangladeshi children with pneumonia.

Conclusion:

The result of our study indicates that TB is common in children presenting with pneumonia in a TB endemic setting such as Bangladesh and X-pert MTB/RIF assay using gastric aspirates demonstrated an additional diagnostic value for detection of pulmonary TB. Xpert MTB/RIF assay can assist in fast diagnosing childhood pulmonary tuberculosis especially patients presented with fever more than one week, malnutrition and having contact with TB patient.

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