The Professional Medical Journal
www.theprofesional.com

DOI: 10.17957/TPMJ/17.3779

ORIGINAL PROF-3779

TUBERCULOUS PERICARDITIS AND PLEURITIS;

GENEXPERT ® TECHNOLOGY A BREAKTHROUGH FOR DIAGNOSIS IN LESS THAN TWO HOURS

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Article received on:
14/12/2016
Accepted for publication:
16/03/2017
Received after proof reading:
06/05/2017

ABSTRACT… Background: Diagnosis of Tubercles Pericarditis and Pleuritis remains the greatest challenge for clinicians. WHO has recommended GeneXpert MTB/RIF assay as a screening test for substitution of conventional methods for the initial diagnosis and prognosis of the extra pulmonary and pulmonary tuberculosis in developing countries. **Objectives:** To find out the diagnostic validity of GeneXpert assay for detection of Myco-bacterium tuberculosis in the pericardial and pleural effusions samples, keeping MTB culture as "Gold Standard". **Material and Methods:** Total number of 286 samples of effusions (pericardial 128, pleural 158) were received, and processed for Zn smear microscopy, LJ culture, GeneXpert MTB/RIF assay according standard protocols. Efficacy for the detection of MTB was evaluated comparatively. **Results:** Out of 286effusions samples AFB was detected by Zn smear in 11 (3.8%) samples while GeneXpert detected MTB in 43 (15.0%) and LJ culture 51 (17.8%). Zn smear showed sensitivity 18.2%, specificity, 98.1%, Positive predictive value 81.8%, Negative predictive value 85.4 %, in comparison GeneXpert showed high sensitivity 84.3%, specificity 100%, with Positive predictive value 100%, and Negative predictive value 96.7%. **Conclusion:** GeneXpert assay is innovative tool in resource limited settings for prompt detection of MTB along with drug résistance. It is definitely an attractive point of care test, with High sensitivity and specificity along with turnout time of two hours which facilitates timely diagnoses and appropriate management of tubercle Pleuritis and Pericarditis.

Key words: GeneXpert MTB/RIF assay, Pleural effusions, pericardial effusion LJ culture.

Article Citation: Mahmood H, Zaib T, Maken ZH, Waqar A, Hassan Y, Mujtaba H, Mutaza F, Noor e Maham. Tuberculous pericarditis and pleuritis; genexpert ® technology a breakthrough for diagnosis in less than two hours. Professional Med J 2017;24(5):656-664. **DOI:** 10.17957/TPMJ/17.3779

INTRODUCTION

Despite molecular technological advances in diagnostic methodologies reduction and eradication of Tuberculosis (TB) still remains a distant goal for clinicians. TB is known to be a disease of mortality & morbidity worldwide. The statics of World Health Organization (WHO) has emphasized on the rapid diagnostic strategies and effective treatment of TB has extremely reduced mortality by 47% since 1990, yet TB remains a major source of death, especially in developing countries.[1]

TB caused by myco-bacterium tuberculosis manifestsitselfintwoforms,pulmonarytuberculosis (PTB) or extra-pulmonary tuberculosis (EPTB). Pulmonary TB is the commonly involving lungs while extra pulmonary TB involves lymph nodes, bone and joints, kidneys, intestine, abdominal and serious membranes like plural, pericardial and meninges.[2]

Globally, among 9.6 million reported TB patients in 2012, estimated 15% were of EPTB while European Center for Disease prevention and Control euro surveillance report mentioned that 22% of notified TB patients in Europe were EPTB.[3] Tubercles pleural effusion is well-known site of EPTB.[4] Tubercular Pericardial effusion is also one of the common manifestation of EPTB occurring in 1- 8% patients.[5] Tuberculosis has been known a cause of acute Pericarditis in 60-80% of the patients in the developing world.[5] pericardial tuberculosis can be differentiated clinically from other causes by using Tygerberg scoring system.

For the diagnosis of tubercular pleural and pericardial effusion, Conventional methods including ZN smear microscopy and LJ culture are available in low to middle income countries. Although ZN staining microscopy is rapid and cheap, however it is less sensitive for diagnosis of EPTB, because of pucibaciliary nature of samples and non-uniform circulation of MTB. LJ Culture is "Gold standard" methods, but its long turnaround time of 2-6 weeks, as well as complexity of procedure demand highly skilled staff along with bio-safety level III lab, limits its applicability for its routine use as diagnostic test.

For EPTB diagnosis, last few decades have witnessed the advancement of molecular techniques, with very good predictive value (PPV:

98–99%).[7,8] Moreover field of TB diagnosis is revolutionized by targeting specific genes or gene segments, and have shortened the turnaround time of detection from weeks to days and days to hours.[8] Precise and accurate TB diagnosis by new molecular tests necessitates specialized infrastructure of laboratory with highly skilled and efficient staff, demanding high cost, limits their use in resource constrained settings.[7]

In 2010, WHO recommended the implementation and the use of a new technology GeneXpert MTB/RIF assay as a substitution over conventional techniques.[9] Later on In October 2013 again WHO dispensed the importance of use of this novel technique for the rapid detection of tuberculosis infection among pediatric and extra-pulmonary cases.[10] Cepheid GeneXpert system is innovative semi-automated real-time PCR nucleic acid amplification technology, which can simultaneously detect MTB and RIF's resistance in less than two hour. Molecular beacon technology and ultrasensitive hemi nested PCR are basis of GeneXpert system.[11] As It is fully closed system, hence there is minimal risk of any type of contamination and biohazard. It also does not require high expertise because of very simple software based handling of the instrument.

A large body of literature is available regarding the role of GeneXpert for the diagnosis of EPTB including Pleuritis, but a paucity of evidence exists concerning its use in Tubercular Pericarditis for the detection of MTB. Thus Present study was planned to highlight the role of GeneXpert technology and to determine its validity for its usage as future diagnostic tool for Tubercular pericardial and pleural effusions.

METHODOLOGY

Ethical approval

Study protocols were approved from institutional board of ethical certification Allama Iqbal medical college & Jinnah hospital Lahore (AIMC&JHL).

Clinical specimens

A total of 286 specimens including 158 pleural and 128 pericardial fluids samples were received from pulmonary and cardiology department of tertiary care hospital Lahore Pakistan, during January 2014 –august 2016.Samples were selected on the basis of i) clinical presentation ,ii) relative lab investigation, iii) echocardiography, iv) radiological finding. Previously diagnosed TB cases and patients on anti-tuberculosis therapy (ATT) were excluded. All these samples were processed at pathology department Myco-bacteriology laboratory (AIMC&JHL), which is among one of the largest referral center in Punjab Pakistan.

Every specimen was processed for Ziehlneelson (ZN) smears microscopy according to WHO[12] GeneXpert MTB/RIF assay had been performed directly in compliance with the manufacturer's SOP's.[13] LJ cultures were processed and reported according to standard guidelines.[14]

QUALITY CONTROL & QUALITY ASSURANCE

ZN Smear

Positive and negative control slides were prepared and stained with every batch. Every slide was checked by two experienced Medical Laboratory Technologist by using light microscope. Random positive and negative, doubtful cases were rechecked by highly experienced senior microbiologists for quality assurance purposes.

LJ Culture

culture media quality and mycobacterium growth was confirmed by using American type culture collection (ATCC) strains of H_{37}rv. a bottle LJ media was inoculated with sterile water as negative control.[15]

GeneXpert Assay

*Bacillus globigii*spores has been used as an internal sample processing and PCR control and this assay is multiplexed with MTB assay [16]

Data Presentation

SPSS 21.0 was used for determination of validity of GeneXpert& Zn smear microscopy, in terms of Sensitivity, specificity, positive predictive value (PPV) negative predictive value (NPV) of ZN Smear had been calculated as followed.

RESULTS

Out of total 286 specimens pericardial fluids and pleural fluids were 44.7% (n=128), 55.3% (n= 158) respectively. Mean age was 44±10.2 years while Males and female were 190 (66.4%) and 96(33.6%) respectively.

Figure-1 Shows Frequency distribution of tuberculosis positive cases detected by different techniques. LJ culture being "Gold standard" for the diagnosis of pulmonary and extra pulmonary tuberculosis, detected Maximum number of MTB in total samples 51 (17.8%), 33 (20.8%) in pleural and 18 (14.0%) in pericardial fluids. It was followed by GeneXpert MTB/Rif assay with detection of MTB in 43 (15.0%) out of total samples, pleural 30 (18.9%) and pericardial 13 (10.1%). A low numbers of positive cases were identified by routinely used conventional technique Zn smear microscopy. AFB was detected in 11 (3.8%), pleural fluid 8 (5.0%) and in pericardial fluid 3(2.2%)

Table-I depicts the diagnostic validity of gene expert assay for the purpose of detection of MTB in the pericardial and pleural fluid keeping LJ culture as gold standard. It was seen that the sensitivity of GeneXpert for pericardial fluid was 72.2%, specificity 100%, PPV 100% and NPV 95.6% while for pleural fluids the sensitivity, specificity, PPV and NPV was 90%, 100%, 100% and 97.6% was found respectively. Diagnostic validity of GeneXpert for detection of MTB in effusion overall was also determined in this study and it was seen that it has a sensitivity of 84.3%, specificity 100%, PPV 100% and NPV of 96.7% respectively for total samples.

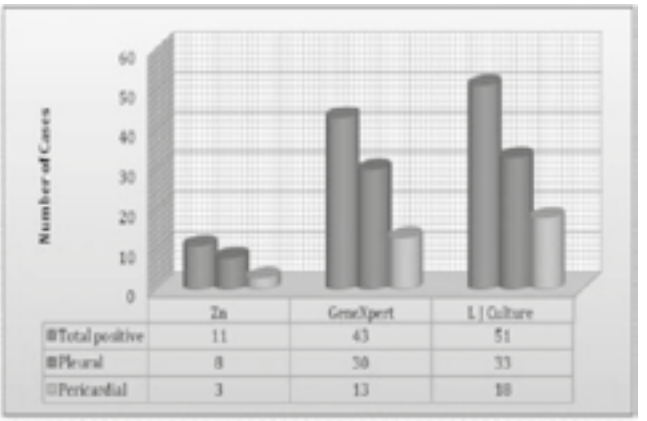

Figure-1. Frequency distribution of tuberculosis positive cases detected by different techniques (n=286).

Samples type	Technique		LJ culture +ve	LJ culture -ve	Total	Sensitivity	Specificity	PPV	NPV
Pericardial fluids	Gene Xpert	+ve	13	0	13	72.2%	100%	100%	95.6%
		-ve	5	110	115				
Total			18	110	128				
Pleural fluids	Gene Xpert	+ve	30	0	30	90.0%	100%	100%	97.6%
		-ve	3	125	128				
Total			33	125	158				
Combine	Gene Xpert	+ve	43	0	43	84.3%	100%	100%	96.7%
		-ve	8	235	243				
Total			51	235	286				

Table-I. diagnostic validity of GeneXpert Assay

The diagnostic validity of Zn smear microscopy for the purpose of detection of AFB in pericardial and pleural fluid keeping LJ culture as gold standard is shown in Table-II. It was seen that the sensitivity of Zn smear for pericardial fluid was 11.7%, specificity 99.0%, PPV 66.6% and NPV 88.0% while for pleural fluids the sensitivity, specificity, PPV and NPV was 21.8%, 99.2%, 87.5% and 83.3% respectively. Regarding, Diagnostic validity of Gene Zn smear for detection of AFB in effusions overall, it was seen that it has a sensitivity of 18.3%, specificity 99.1%, PPV 81.8% and NPV of 85.4% respectively for total samples.

Samples type	Technique		LJ culture		Total	Sensitivity	Specificity	PPV	NPV
			+ve	-ve					
Pericardial fluids	Zn smear	+ve	2	1	3	11.75	99.0%	66.6%	88.0%
		-ve	15	110	125				
Total			17	111	128				
Pleural fluids	Zn smear	+ve	7	1	8	21.8%	99.2%	87.5%	83.3%
		-ve	25	125	150				
Total			32	126	158				
Combine	Zn smear	+ve	9	2	11	18.3%	99.1%	81.8%	85.4%
		-ve	40	235	275				
Total			49	237	286				

Table-II. Statistics of Zn smear microscopy

Table-III. Presents the diagnostic validity of GeneXpert in Zn smear negative pericardial and pleural fluid samples. It was seen that the sensitivity of GeneXpert Smear negative for pericardial fluids was 68.7%, specificity 100%, PPV 100% and NPV 95.6% while for pleural fluids the sensitivity, specificity, PPV and NPV was 88.4%, 100%, 100%, and 97.6%, respectively. Diagnostic validity of Gene Zn smear for detection of AFB overall was also determined in this study and it was seen that it has a sensitivity of 80.9%, specificity 100%, PPV 100%, and NPV 96.6% respectively for total samples.

Samples type	Technique		LJ culture		Total	Sensitivity	Specificity	PPV	NPV
			+ve	-ve					
Pericardial fluids	GeneXpert	+ve	11	0	11	68.7%	100%	100%	95.6%
		-ve	4	110	114				
Total			15	110	125				
Pleural fluids	GeneXpert	+ve	23	0	23	88.4%	100%	100%	97.6%
		-ve	2	125	127				
Total			25	125	150				
Combine	GeneXpert	+ve	32	0	32	80.9%	100%	100%	96.6%
		-ve	8	235	243				
Total			40	235	275				

Table-III. statistics of GeneXpert in Smear negative samples

Figure-2 Showed sample-wise frequency distribution of MDR cases detected by GeneXpert. Among 13 MTB positive pericardial fluids detected by GeneXpert, 2 (15.3%) were drug resistance and out of 30 MTB positive pleural fluids 9(30%) were drug resistant. Out of total 43 GeneXpert positive samples 11(25.5%) were Multidrug resistance tuberculosis (MDR).

DISCUSSION

Diagnosis of tuberculosis has always been a challenge for health services and clinicians. Despite the availability of anti-TB treatment for more than 60 years, it is still a cause of an unacceptably high mortality rate. EPTB is also responsible for life threatening consequences and to overcome this problem there is an urgent

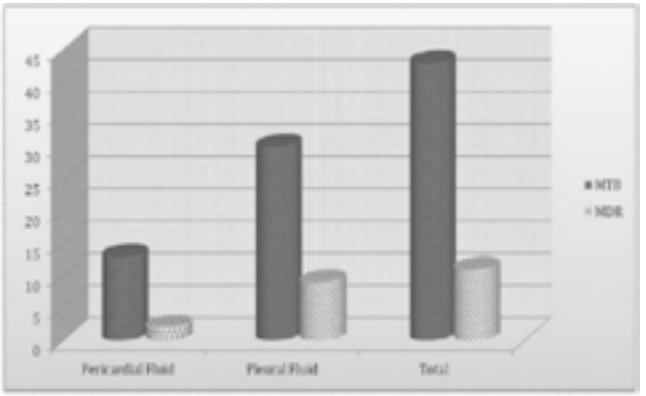

Figure-2. Sample-wise frequency distribution of MDR cases detected by GeneXpert

a breakthrough technique for the diagnosis of EPTB, but limited literature is available about its diagnostic validity in effusions. The present study highlighted the role of Gene expert for rapid diagnosis of tuberculosis Pericarditis and Pleuritis in terms of sensitivity, specificity, PPV, NPV with LJ culture being "Gold standard". We also evaluated sensitivity and specificity of Zn smear microscopy in pleural and pericardial effusions for detecting AFB.

Regarding ZN smear, Overall sensitivity of 18.3% for both the sample with specificity of 99.1%, was observed. While sensitivity and specificity of 21.8% and 99.2% was seen for pleural fluids and 11.7% and 99.2% respectively for pericardial fluids was obtained. The results of our study are significantly higher as compared to those in study from spain in which a sensitivity of 7.3% and specificity of 100% was achieved by Zn smear microscopy in tubercles pleural effusion. The difference in the results might be attributed to the difference in the endemicity of the disease in the two regions with Pakistan being a high endemic region as compared to Spain.[18]

Over all MTB positive rate was 17.8% detected by LJ culture which is comparable with another study conducted in similar province showing 18.1% MTB positive rate among EPTB.[19] This burden is even greater in countries with high burden of TB along with HIV shown by the results of study conducted by Pandie et al. which reported a MTB positive rate of about 49%.[20]

It was observed that GeneXpert has a high sensitivity and specificity for detection of MTB in effusions for diagnosis of tuberculouseffusion i.e. 90% and 100% respectively. According to the report published by WHO the pooled sensitivity of GeneXpert in pleural fluid is 43.7%, these results are very lower then present study due to the use of different gold standards in various studies included in this meta- analysis.[23]

A recent meta-analysis reported the pooled sensitivity and specificity of GeneXpert for pleural fluid as 46.4%and 99.1%, respectively, compared with those of pleural fluid mycobacterial culture[24] Another meta-analysis conducted on 13 studies reported pool sensitivity of GeneXpert as 37.0% for pleural fluids.[25] Later on a systematic review conducted on 24 studies reported pooled sensitivity and specificity of GeneXpert as 51.4% and 98.6%, respectively in pleural effusion.[26]

Results of these meta-analyses are different due to difference in burden of disease, patients' selection criteria and methodologies.

Study	Years	TP	FP	FN	TN	Sensitivity	Specificity	REF
Friedrich et al	2011	5	0	4	16	56.0%	100%	27
Hanif et al	2011	3	0	0	8	100%	100%	28
Vadwai et al	2011	5	0	5	19	50%	100%	29
Al-Ateah et al	2012	3	0	0	10	100%	100%	30
Coleman et al	2014	9	0	4	37	69.0%	100%	31
Du et al	2015	25	0	7	94	78%	100%	32
Rufai et al	2015	23	0	19	120	55%	100%	33

Table-IV. previous studies reported Sensitivity and specificity of GeneXpert in tubercular pleural fluids

Another best diagnostic tool for pleural TB is pleura biopsy which is an invasive procedure with sensitivity ranging from 93 to 100%[34,35] followed by ADA level which has a variable sensitivity ranging from 47-100%.[36] This make GeneXpert a favorable choice for the diagnosis of tubercular pleuritis because of higher sensitivity, specificity, rapidity and simplicity of the procedure

There is limited information on diagnostic utility of this test in particular for pericardial fluid which is a highlight of this study. The results of this study showed that GeneXpert exhibit a high diagnostic validity for detection of MTB in pericardial fluid with a sensitivity 72.2% and specificity 100%. Pandie et al.[20] which showed a similar specificity of 100% but a sensitivity of 63.8% which is less as compared to our results because of inclusion of a large proportion of immune-compromised HIV patients in that study. Moreover, the strict clinical diagnostic criteria for inclusion of patients can also lead to the higher sensitivity reported by current study. Cegielski*et al*[37] evaluated diagnostic efficacy of PCR pericardial fluid (n=13) and pericardial tissue (n=15) from 20 patients, and showed that accurate diagnosis of TB was correctly made in 81% (n=13).

For the provisional diagnosis and initiation of empirical therapy of tubercular pericarditis, Tygerberg scoring system is usually applied in clinical settings. However, due to increase in multidrug resistance TB around the globe, desirable treatment success rate is not achieved with first line drug making efficacy of therapy questionable. The application of GeneXpert gives additional information regarding drug resistance thus optimizing and increasing the effectiveness of therapy. The result of this study has pinpointed 25.5% MDR cases, 15.0% in pericardial and 30.0% in pleural fluids. All these drug resistance cases can be timely managed according to the protocol of drug resistance tuberculosis to achieve a higher treatment success rate in minimum time.

Smear negative

Almost 3.553 GeneXpert instruments and 8.8 million cartridges were provided from WHO at the end of 2014 among 110 high burden and low-income countries.[38] it is expected that there will be scale up of this brilliant technology in future, which will help in reducing not only the disease burden, but also the cost of diagnosing and managing the patients. WHO has recommended in its revised guidelines that GeneXpert should be used as an integral part for diagnosing tuberculosis in high burden countries this assay, as well as it will be a part of revised guidelines in high burden countries.

In a study from South Africa in 2012, it is documented that GeneXpert assay has replaced the Zn smear microscopy for rapid detection of mycobacterium tuberculosis, and has been implemented on a very large scale among each and every sector of the country.[39]

CONCLUSION

Considering the diagnostic validity of GeneXpert along with detection of drug resistance in 2 hours turnout time, GeneXpert assay is a boon for resource limited settings making it an attractive tool for accurate diagnosis of tubercle Pleuritis and Pericarditis with high sensitivity and specificity point of care testing. This will facilitate timely management and appropriate treatment of patients to reduce the mortality and morbidity.

Limitations

One limitation in these study was that majority of the respondents whom I approached were not interested in participation. This did not allow the research to be versatile in terms of finding. The results may have diverse if there were perceptions from a larger sample size. Participants considered in this study do not represent the general population of tuberculosis patients and thus this study is limited to one city or area of Pakistan. These findings are principally viewed through the laboratory lens. The number of males in the research was greater with only female participants.

Acknowledgments

The researchers are thankful for providing the free kits. We are also grateful to the Jinnah Hospital

staff, Allama Iqbal medical college, Ganga Ram Hospital for providing assistance in this research. Last but not least, we are grateful for all the participants and the stake holders for their co-operation.

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CORRECTION

The amendment of the Professional Vol: 24, No.02 (Prof-3711) page 335 titled: "Upper gastrointestinal bleeding; Endoscopic findings in patients" is as under;

INCORRECT

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