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DIAGNOSTIC ACCURACY OF XPERT-MTB/RIF ASSAY IN GENITOURINARY TUBERCULOSIS

Urology

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ABSTRACT

Genitourinary tuberculosis is still a major health problem in many developing countries including India and the diagnosis requires the availability of diagnostic tools that allow the rapid detection of M. Tuberculosis.

Objective: To determine the sensitivity and specificity of Xpert MTB/RIF Assay in the diagnosis of genitourinary tuberculosis.

Methods: A prospective study wherein the urine samples of patients with suspected GUTB, were subjected to XpertMTB/RIF assay and AFB culture. The XpertMTB/RIF assay was compared with AFB urine culture which is considered gold standard and sensitivity and specificity was calculated.

Results: The results of XpertMTB/RIF assay for 231 samples were compared with those of cultures. The sensitivity of the XpertMTB/RIF assay was 83.3% and the specificity was 100%.

Conclusion: The GeneXpert assay is a useful rapid diagnostic test for both pulmonary and EPTB including GUTB.

KEYWORDS

Genitourinary tuberculosis; Xpert MTB/RIF; Diagnostic accuracy.

Introduction

The term 'genitourinary tuberculosis' was introduced by Wildbolz in 1937, and since then, renal and epididymal tuberculosis were considered together as the local manifestation of the same blood-borne infection[1]. Genitourinary tuberculosis (GUTB) is still a major health problem in many developing countries including India and has been declared by World Health Organization (WHO) as 'public health emergency' in 1993[2,3]. The incidence of combined pulmonary extrapulmonary cases and extrapulmonary TB alone comprise 12% and 20-25% of the total disease burden respectively[1]. Amongst extrapulmonary TB, GUTB accounts for 4% of the load[3]. In comparison to the patient's complaints, the sequel of genitourinary TB is volcanic and requires proper understanding.

Incidence

Genital tract tuberculosis The most common form of extrapulmonary TB is genitourinary disease, accounting for 27% (range, 14 to 41%) worldwide. In India the incidence of genital tuberculosis is nearly about 18%[4].

Female genital tract tuberculosis: It is estimated that 1% of infertile women, aged between 20-40 years in United States and 18% in India suffer from genital TB[2]. In females the genital organs commonly affected are as follows: fallopian tube (95-100%), endometrium (50-60%), ovaries (20-30%), cervix (5-15%), myometrium (2.5%) and vulva/vagina (1%)[5].

Male genital tuberculosis: Male genital TB is predominantly associated with tuberculosis of the kidney and prostate, seminal vesicle, epididymis, testes as well as scrotum may occasionally be affected[6].

Urinary tract tuberculosis In general population: In India, the incidence of urinary tract TB comprises 4% of the disease burden[7]. In a study by Venkata et al., 69.4% of urinary tract TB was association with dismorphic kidney disease, with an age of occurrence between 25-77 years and a male to female ratio of 33: 3[8].

Tuberculosis in HIV-infected patients: Currently, amongst the new TB cases detected in India, 5.2% are diagnosed to have HIV (15-49 years) and in an average, 10% of all cases of TB worldwide are HIV-related (1999 data)[9,10].

Tuberculosis in post-transplant patients: The prevalence of post-transplant TB varies from 1% in Germany to 9.5-14.7% in India, with 5- 50 times cumulative risk of infection than in the general population[11].

Tuberculosis in children with nephrotic syndrome: The conventional diagnostic tests, are often unhelpful in these children, and need high index of suspicion, as in a study by Gulati et al., 9.3%, amongst a total of 300 children with nephrotic syndrome had renal tuberculosis[12].

Renal TB should be suspected and treated if the tubercle bacillus is identified microscopically in a urine specimen[14]. Demonstration of acid-fast bacilli (AFB) on Ziehl-Nielsen (ZN) stain examines the patience and diligence of the pathologists. The ZN stain identifies organism at a level of 5000-10,000 bacilli/ml of sputum with a sensitivity of detection of 22-81%[1]. In Indian studies TB culture is positive in only 30-40% of urine samples[13]. So a negative urine culture report should not rule out a possibility of TB and in these situations, polymerase chain amplification for bacterial nucleic acid provides an effective and rapid detection method for urinary TB in both pre- and post-treatment patients[14]. The World Health Organization (WHO) has endorsed the implementation of GeneXpert MTB/RIF assay for national tuberculosis programs in developing countries[17]. The Xpert MTB/RIF (Cepheid Inc.) is an automated, user friendly and rapid test based on nested real-time PCR assay and molecular beacon technology for MTB detection and RIF resistance. The results are obtained within a short period of 2 hours[15]. Further on, the technique is not prone to cross-contamination, requires minimal biosafety facilities and has a high sensitivity in smear-negative pulmonary TB[16,18-20]. Its effectiveness in EPTB is also documented[15,21]. The diagnosis of EPTB is often difficult to establish, considering that number of bacteria in specimens is often very low, a collection often requires invasive procedures, and it is not easy to obtain multiple samples. In this scenario GeneXpert is a potentially useful tool for extrapulmonary specimens.

Objectives

1. To determine the sensitivity and specificity of Xpert MTB/RIF Assay in the diagnosis of genitourinary tuberculosis.
2. To compare the accuracy of Xpert MTB/RIF Assay with that of culture

Materials and Methods

This prospective study was conducted in the Department of Urology, St. John's Medical College Hospital between July 2015 and December 2016. The study group comprised of 231 patients (more than 18 years of age) suspected of having symptoms of GUTB. Patients who were proven MDR TB were excluded from the study. The study was approved by institutional Ethical committee and written consent was obtained from each patient included in the study.

The urine samples of all the patients with suspected GUTB were subjected to Xpert MTB/RIF assay and AFB culture. The final report of XpertMTB/RIF assay was compared with AFB urine culture which is considered gold standard and sensitivity and specificity was calculated.

1. ZN staining for smear microscopy was done following the WHO recommended protocol[23].
2. Culture on Lowenstein–Jensen (L.J) media: Culture was put up after decontamination of the urine samples on LJ media slopes following the standard protocol[24]. LJ culture used as the reference method.
3. XPert MTB/RIF assay: Samples were concentrated by cyto-centrifugation at 3000g for20 minutes and the deposit was processed as follows. [samples were processed directly from Xpert MTB/RIF test, according to manufacturer's protocol.] Sample reagent is added in a 2:1 ratio to processed urine in 15 ml falcon tube and the tube is manually agitated twice during a 15 minute incubation period at room temperature. Then 2ml of the inactivated material is transferred to the test cartridge by a sterile disposable pipette (provided with kits). Cartridges are loaded into the GeneXpert. The interpretation of data from MTB/RIF tests is software based and not user dependent.

The sensitivity, specificity, positive predictive value(PPV) and negative predictive value(NPV) of each test was calculated according to the respective formulae.

Results

A total 231 specimens obtained from patients hospitalized at St. John's Hospital, Bangalore were included in this study. All specimens were analyzed by microscopy, culture, and molecular detection with the Xpert MTB/RIF assay. The results are reported in Table 1.

Eighteen(7.79%) of the 231 specimens were positive for MTBC culture.

AFB smear microscopy could detect only 50% of the MTBC culture-positive specimens (9/18 specimens).

The Xpert MTB/RIF molecular assay was able to detect 83.3% of the MTBC culture- positive specimens (15/18 specimens).

Table 1: Comparison of results of various methods.

Culture Result	Total Number	AFB smear result		Xpert MTB/RIF assay result	
		Positive	Negative	Positive	Negative
MTBC	18	9	9	15	3
Negative	213	0	213	0	213
Total	231	9	222	15	216

Sensitivity and specificity of Xpert MTB/RIF molecular assay: Using culture as the gold standard, the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for the Xpert MTB/RIF molecular assay and AFB testing were calculated for all the specimens; the results are reported in Table 2.

The sensitivity and specificity of the Xpert MTB/RIF assay were 83.3% and 100%, respectively. The negative predictive value (NPV) and positive predictive value (PPV) of the Xpert MTB/RIF assay were 98.6% and 100%.

Table 2: Sensitivity, specificity and predictive values of various methods.

Method	Sensitivity (%)	Specificity (%)	NPV(%)	PPV(%)
AFB Smear testing	50	100	95.9	100
Xpert MTB/RIF Assay	83.3	100	98.6	100

Discussion

In our study, the diagnostic performance of the Xpert MTB/RIF molecular assay has been evaluated and its ability to detect the presence of MTBC. The sensitivity and specificity of the Xpert MTB/RIF assay in detecting MTBC were shown to be very high, and the results of this study indicate that this assay can be a useful tool for the rapid diagnosis GUTB. Culture is used as the gold standard for the diagnosis of TB. In contrast, smear microscopy to detect acid-fast bacilli in clinical specimens is rapid and inexpensive but shows low sensitivity[25]. In our study, the sensitivity of AFB smear microscopy was 50%, while the Xpert MTB/RIF assay was able to detect correctly about 83.3% showing greater sensitivity but the same rapidity as AFB smear microscopy. The sensitivity of the Xpert MTB/RIF assay was comparable to that obtained in other recent studies[16-18].

In Shagufta et al [22], study evaluated the diagnostic accuracy of Xpert MTB/RIF assay both for pulmonary and EPTB cases and compared it with the conventional techniques. Out of 245 TB suspects 111 (45.3%) were Xpert positive which included 85 (76.6%) ZN smear positive and 26 (23.4%) smear negative cases. Here, the on time Xpert MTB/RIF assay could diagnose an additional 23.4% case along with an added advantage of much lower turnaround time.

In another study by Boehme et al. reported 77% sensitivity of Xpert MTB/RIF assay in smear negative samples[30]

Bates, et al. study reported a better detection rate with Xpert when compared to smear microscopy and culture[29]. In harmony with this study Zeka et al.[20] also reported 100% specificity of MTB/RIF test in 110 clinically and microbiologically diagnosed tuberculosis patients.

In a study by Hillemann et al. , EPTB samples were reported to have a sensitivity and specificity of 77.3% and 98.2%, respectively indicating a higher sensitivity of Xpert as it could detect some of the culture negative cases as well[31].

GUTB can be challenging to diagnose, since the number of bacteria in the urine specimen is often low because of the paucibacillary nature of the disease. The high sensitivity and specificity highlight the Xpert MTB/RIF assay as an adequate diagnostic method.

In our study, the Xpert MTB/RIF assay correctly identified more than 80% of MTBC directly from clinical samples, indicating that this molecular assay can improve the diagnosis of GUTB.

Considering the ease of handling the GeneXpert assay, the implementation of TB diagnosis is made feasible in many laboratories especially in countries with high incidence of GUTB.

Conclusion

The GeneXpert assay is a useful rapid diagnostic test for both pulmonary and EPTB including GUTB as it has greatly shortened the time of detection up to two hours as compared to other techniques[14,23]. This advantage is translated into clinical management for patients with smear negative TB as the Xpert assay reduces the time to start treatment for several weeks to just a few days.

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