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A study on urinary PCR in the detection of mycobacterium tuberculosis in patients with genitourinary tuberculosis and to compare its sensitivity with conventional culture methods

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Abstract
Background: In genitourinary tuberculosis the diagnosis is usually delayed because of its non-specific presentation and variable radiographic appearance which often mimics other pathological lesions, with the consequence that a number of patients present with non-functioning kidneys, ureteral stricture and shrunken bladders.
Aim & Objective of the study: The main of the present study is to evaluate the role of urinary PCR in the detection of mycobacterium tuberculosis in patients with a clinical suspicion of genitourinary tuberculosis and to compare its sensitivity with urine for AFB smear, urine for Mycobacterium tuberculosis culture and bladder biopsy.
Materials and Methods: This is a prospective study of patients with a diagnosis of genitourinary tuberculosis who underwent treatment in Nizam's institute of medical sciences between September 2016 to December 2017. 60 patients with a diagnosis of genitourinary tuberculosis who underwent treatment were taken initially into the study.
Results: In the present study: Urine for AFB staining was positive in 20(35.05%) patients, urine for MTB culture was positive in 28 (49.12%) patients. Urinary PCR to identify the mycobacterial DNA was positive in 16(61.40%) of 57 clinically suspected cases. The urinary PCR was falsely positive in none and falsely negative in 22(38.59%) patients. Results revealed that, kidney is involved in 26 cases and is the most common organ involved in our study along with Urethra (26 cases) and bladder (24 cases), urethra (8 cases). Epididymis was involved in 4 cases. Overall Radiological abnormalities suggestive of GUTB were found in 46(80.7%) cases. Overall GUTB was identified by direct identification of bacilli by Urine PCR/Urine for AFB STAIN/ urine for MTB Culture in 92.98% of the cases. It was identified by HPE also in 77.77%. Strong clinical and radiological suspicion with NO evidence of bacilli was present in 7.02% cases.
Conclusion: The present study concluded that, the sensitivity of Urinary PCR is high (61.40%) when compared to the sensitivities of urine for AFB staining (35.08%), MTB culture (49.12%) and bladder biopsy (41.66%).

Keywords: polymerase chain reaction, genitourinary, mycobacterium tuberculosis, acid fast bacilli (AFB)

Introduction
Tuberculosis has remained a major public health problem since the dawn of the civilization and continues to impose a major financial burden on the society.
Genitourinary tuberculosis is a Paucibacillary type where microbiological evidence of infection is difficult to obtain with conventional methods. Polymerase chain reaction is a technique that can be used to amplify a specific DNA genomic sequence, where by the presence of an extremely small number of bacteria can be detected in a case of Genitourinary TB within 24 – 48 hours. In genitourinary tuberculosis the diagnosis is usually delayed because of its non-specific presentation and variable radiographic appearance which often mimics other pathological lesions, with the consequence that a number of patients present with non-functioning kidneys, ureteral stricture and shrunken bladders. These changes can be avoided if the diagnosis is made early and treated effectively.
In view of these considerations, the present study has been taken up to examine these considerations further and to evaluate the role of urinary PCR in the detection of mycobacterium tuberculosis in patients with a clinical Suspicion of genitourinary tuberculosis and to compare its sensitivity with urine for AFB smear, urine for Mycobacterium tuberculosis culture and bladder biopsy.

Materials and Methods
Place of study and Duration
This is a prospective study of patients with a diagnosis of genitourinary tuberculosis who underwent treatment in Nizam's institute of medical sciences between September 2016 to December 2017.

Study population
60 patients with a diagnosis of genitourinary tuberculosis who underwent treatment were taken initially into the study. 3 patients were lost to follow up after initial visits. These patients were excluded from the study.

Inclusion criteria
All the patients reporting to the hospital with proven genitourinary tuberculosis or diagnosed after coming to the hospital and were treated as inpatients were included in the study.

Exclusion criteria

- Patients who were not admitted to the hospital were excluded from the study.
- Patients with less than 6 months of follow up were also excluded from the study

History, physical examination, laboratory and radiological investigations were done on the patients, and the primary focus of the disease and the organs involved were determined. All the patients received treatment as indicated.
The laboratory investigations done included urinalysis, full blood count with estimation of erythrocyte sedimentation rate (ESR), RFT, Mantoux (tuberculin) skin test, and screening for HIV. Urine PCR for Mycobacterium tuberculosis DNA, Urine for AFB staining and mycobacterial cultures were obtained on first morning sample on 3 consecutive days in all cases.
Radiological evaluation included Chest X-ray, X-ray Kub & Ultrasound KUB in all cases. CT scan was done in most of the cases. IVU was done in some cases. DTPA was obtained as and when necessary. Cystoscopy and bladder biopsy were done wherever indicated.

Direct Microscopic Examination

For Urine AFB smear at least 3 early morning urine samples should be analyzed. A bacterial load of 5000 organisms/ml is needed for positive smear [1]. In case of increased day/night urinary frequency, at least 8 hours of collection of urine is required for AFB smear. Routine ziehl neelsen staining has a sensitivity and specificity of 60-70% and 90-95% respectively. Auramine / Rhodamine staining with fluorescent microscopy increases sensitivity by 10-15% as compared to ZN staining [1]. Smear positivity alone should not be considered as diagnostic of tuberculosis since chronic infections due to non-tubercular mycobacteria (NTM) is not uncommon and do not usually respond to the conventional ATT. In the absence of AFB culture or other molecular assays, there is high chance of branding a non-responder as non-compliant or resistant case of tuberculosis [2].

Culture

AFB culture by conventional Löwenstein- Jensen (LJ) medium is still the gold standard and has a sensitivity and specificity of 80-85% and 98% respectively. The main drawback of this technique is that it requires 6-8 weeks for the results. Three types of media are used Egg based (LJ), Agar based (Middlebrook 7H10 or 7H11) or Liquid based (Middlebrook 7H9) [1]. Radiometric culture methods give results in 2-3 weeks and are equally sensitive (replaced by MGIT nowadays). Mycobacterial Growth Indicator Tube (MGIT) uses Middle brook 7H9 broth with oxygen sensitive fluorescent sensor at bottom. Positive signals are obtained in 10-12 days.

Nucleic acid amplification tests - Polymerase chain reaction (PCR)

NAAT- PCR methods have sensitivity of 70-100% and specificity of 80-100 [3]. PCR makes millions of identical copies of a specific DNA sequence (a gene, a part of a gene, a stretch of nucleotides with a known DNA sequence). A specimen that may contain the DNA sequence of interest is heated to denature double stranded DNA. Specific synthetic oligonucleotide primers bind to the unique DNA sequences and a heat stable DNA polymerase (Thermus aquaticus) extends the primer to create a complete & complimentary strand of DNA. Process is repeated sequentially 25-40 times, thereby creating millions of copies of target sequence. The amplified sequence is then detected by agarose gel electrophoresis [3].

Histopathology

Histopathology shows findings consistent with TB in 38.3% of GUTB cases in developed countries and 21.9% of cases globally. Because urine cultures are sometimes negative, tissue biopsy can aid the diagnosis of GUTB [4]. Although mycobacteria are often not seen, the finding of caseating granulomas in the appropriate clinical context can help establish a diagnosis of GUTB.

Results

Table 1: Comparison of Urinary PCR with Urine for AFB Smear, Urine for MTB Culture, and Bladder Biopsy

Investigation	Urine For PCR	Urine For AFB	Urine For MTB Culture	Bladder Biopsy
Cases tested	57	57	57	24
Positive	35	20	28	10
Negative	22	37	29	14
Sensitivity	61.40%	35.08%	49.12%	41.66%

Urine for AFB staining, mycobacterial cultures and PCR were obtained on first morning sample on 3 consecutive days for all the patients. Urine for AFB staining was positive in 20 (35.05%) patients, urine for MTB culture was positive in 28 (49.12%) patients. Urinary PCR to identify the mycobacterial DNA was positive in 16 (61.40%) of 57 clinically suspected cases. The urinary PCR was falsely positive in none and falsely negative in 22 (38.59%) patients.

Table 2: Involvement of organs in Genitourinary Tuberculosis

Anatomical site / Organ	Frequency	Percentage
Kidney only	-	-
Kidney & Ureter	14	24.56%
✓ Kidney and upper ureter	10	
✓ Kidney and lower ureter	4	
✓ Kidney with involvement		
of entire ureter		
Pelviureteric junction	6	10.52%
Ureter only	-	-
Urinary bladder only	10	17.54%
Chronic cystitis	6	
Contracted bladder	4	
Urinary bladder and Ureter	6	10.52%
Urinary bladder, ureter and	6	10.52%
kidney		
Urinary bladder and Urethra	2	3.50%
Urethra	6	10.52%
Epididymis	4	7.01%
Seminal vesicles and Vas	-	-

In this study kidney is involved in 26 cases and is the most common organ involved in our study along with Ureter(26 cases) and bladder (24 cases), urethra (8 cases). Epididymis was involved in 4 cases.6 cases of PUJ obstruction were present out of which 5 cases had non-functioning kidneys. So nephrectomy was done. In 1 case, pyeloplasty was done.

Table 3: Radiological investigations

Investigation	No. of cases	Percentage of Cases
Chest X-ray	57	100%
Ultrasound	57	100%
Intravenous urography	27	47.36%
CT scan	38	66.66%
MRI	10	17.54%
RGU	14	24.56%
MCUG	14	24.56%
DTPA	38	66.66%

Chest X-ray and ultrasound abdomen were done in all cases as a routine. CT scan was done in 38 cases. IVU was done in 27 cases and it showed positive findings in 23 cases and MRI was done in 10 Cases. RGU and MCUG were done in 14 cases where stricture urethra was suspected and it was positive in all 14 cases. DTPA was done in 38 cases. Overall Radiological abnormalities suggestive of GUTB were found in 46 (80.7%) cases.

Table 4: Diagnostic criteria

Investigation	Total	No of cases detected	Percentage
Urine for PCR	57	8	14.03%
Urine for MTB culture	57	4	7.01%
Urine for AFB stain	57	4	7.01%
Urine for PCR & MTB culture	57	14	24.56%
Urine for PCR & Staining	57	08	14.03%
Urine for AFB stain and MTB culture	57	02	3.50%
Urine for PCR,AFB stain & MTB culture	57	02	3.50
Bladder Biopsy &MTB Culture	24	02	8.33%
Bladder Biopsy and AFB Stain	24	02	8.33%
Bladder Biopsy	24	04	16.66%
HPE only	18	02	11.11%
Confirmed on HPE after positivity on AFB/PCR/MTB	18	12	66.66%
Clinical &Radiological suspicion with E/O of Bacilli on AFB/PCR/MTB	57	53	92.98%
Clinical &Radiological suspicion with NO E/O of Bacilli	57	4	7.02%

Overall GUTB was identified by direct identification of bacilli by Urine PCR/Urine for AFB STAIN/ urine for MTB Culture in 92.98% of the cases. It was identified by HPE also in 77.77%. Strong clinical and radiological suspicion with NO evidence of bacilli was present in 7.02% cases.

Discussion

In our study Mycobacterium was detected by Urinary PCR in 61.40% and by urine culture in 49.12% of our cases as compared with 50 to 90% reported in the literature. Narotam sharma *et al.* [5] showed that PCR positivity rate was 30.7 %, followed by culture 8.0 % and AFB smear 1.9 % respectively. We performed bladder biopsy in 24 cases to aid in the diagnosis and positive yield was obtained in 10 cases (41.66%). Wong *et al.* [6] achieved a tissue diagnosis in 18.5% of their cases and reported no adverse effects of bladder biopsy. However Gow *et al.* [7] suggests bladder biopsy should not be carried out unless a malignancy needs to be excluded.

PCR is a technique that can be used to amplify a specific DNA genomic sequence, whereby the presence of an extremely small number of bacteria can be detected [8]. The high sensitivity of PCR is particularly useful in paucibacillary situations. PCR can provide much faster confirmation of the diagnosis (24-48 hrs) than MTB culture [9]. The limit of detectability of PCR may vary from about 10 organisms to as little as 1 bacillus. Urinary PCR is specific for the MTB complex (MTB and M. Bovis) and no crossover reaction occurs with other mycobacteria. In the 57 cases of proven GUTB where PCR was done, it was positive in 35 (61.4%) cases which is low when compared with other studies in the range of 85% to 95%. Urinary PCR is falsely positive in none and false-negative in 38.6% of the samples in our study in contrary to 5-15% reported in the literature [9]. False-negative findings may result from the presence of inhibitors, nonhomogeneous distribution of bacteria in the specimen so that the fraction tested does not contain mycobacteria or low numbers of mycobacteria in the specimen, which decreases the probability of the presence of organisms in the fraction analyzed by PCR [8, 9]. In our study the sensitivity of Urinary PCR is high (61.40%) when compared to the sensitivities of urine for AFB staining (35.08%), MTB culture (49.12%) and bladder biopsy (41.66%).

Diagnostic Criteria

In this study bacilli could be identified separately with urine for PCR in 61.4%, by MTB Culture in 49.12%, by urine for AFB stain in 35.08%. When all the above three are used on all the 57 patients the bacilli identification was there in 53 cases (92.98%) of the cases. The rest of the cases were diagnosed on the basis of histopathology, radiographic and clinical evidence. Majority of the cases (77.77%) in this study were positive on histopathological examination of the operative or biopsy specimen. Narotam sharma *et al.* [5] showed that PCR positivity rate was 30.7 %, followed by culture 8.0 % and AFB smear 1.9 % respectively. We performed bladder biopsy in 24 cases to aid in the diagnosis and positive yield was obtained in 10 cases (41.66%). Wong *et al.* [6] achieved a tissue diagnosis in 18.5% of their cases and reported no adverse effects of bladder biopsy.

Renal TB can result in end-stage renal disease by two mechanisms. First, it can inflict direct insult to renal parenchyma by causing obliterative endarteritis of the intra-renal segmental vessels or secondary renal amyloidosis. Secondly, by the obstruction of pelvi-ureteric junction or multiple infundibular stenoses, it can result in obstructive uropathy [10].

The overall incidence of increased serum creatinine (renal failure) reported in the literature is 24%. Gupta *et al.*. [11] (2006) had reported an incidence of 22.4% in their retrospective analysis of 241 patients. In the study of el

Khader *et al.* [12] (2001) 14% presented with renal failure (mean serum creatinine: 1.8 mg/l). In the study of Benchekroun *et al.*. [13] (1998) renal function was impaired in 32% of patients. In our study patients with serum creatinine above 1.5 mg/dl were considered as having renal failure. Such patients need to be closely followed up as they could develop chronic renal failure necessitating dialysis and renal transplantation. If the patient presents with obstructive uropathy, it is necessary to do an initial diversion in the form of percutaneous nephrostomy and allow sufficient time for the serum creatinine levels to reach a nadir value, before planning any form of definitive intervention [11].

Table 5: Studies investigating renal failure in GUTB

Study	Renal failure percentage
Gupta *et al.*. [11] (2006)	22.4%
Current study	35.08%

In our study past history of pulmonary TB was seen in 6 cases (10.52%). In the study of Smita Chandra *et al.*. [14] (2012) 36% had a previous history of TB. In the study of 101 GUTB patients by Joo Yong Lee *et al.* [15] (2011) 19.8% had history of TB. In the study of Orakwe. J. C *et al.*. [16] (2005) 11.5% of patients had evidence of active concurrent pulmonary tuberculosis radiographs. Lack of evidence for a concurrent or previous pulmonary or other focus of primary infection is however not an unusual finding in patients with genitourinary tuberculosis [17].

Table 6: Studies investigating past h/o pulmonary TB in GUTB

Study	Past history of pulmonary TB (%)
Smita Chandra *et al.* [14] (2012)	36%
Joo Yong Lee *et al.* [15] (2011)	19.8%
Current study	10.52%

In this study all the 57 patients were screened for HIV and none were positive for it. In the study of Orakwe. J.C *et al.* [16] (2005) twenty-two patients out of 31 were screened for HIV and only two patients were positive for it. All the patients (40) in the study of S. Ray *et al.*. [18] (2012) were negative for HIV infection. Smita Chandra *et al.*. [14] (2012) in her study of 25 GUTB cases, HIV was negative in the eight cases in which it was performed.

The World Health Organization believes that the recent upsurge of tuberculosis in the developing world is significantly contributed by the high prevalence of HIV infection as patients with HIV infection are highly predisposed to tuberculosis [19].

Thus the finding of no HIV positive patients in our study may be surprising, but there is also a similar finding for extra-pulmonary tuberculosis in general in Hong Kong [20].

Organ Involvement

Kidney is the most commonly affected organ in GUTB followed by ureter and bladder. In 92% of cases genitourinary tuberculosis is secondary to focus in lungs, lymph nodes, bones and joints and manifests after a long latent period. In this study kidney is involved in 26 cases (45.61%) and is the most common organ involved in our study along with ureter 26 cases (45.61%) followed by bladder in 24 cases (42.10%) and urethra in 8 cases (14.03%). Epididymitis was seen in 4 cases (7.01 %.) PUJ was involved in 6 cases (10.52%) causing obstruction131 history cases of GUTB patients, who were revealed in 2009 – 2011 years in

Siberia, were analyzed by Kulchavenya *et al.*. [21] (2013). The most common form waskidney tuberculosis (74.8%). In study of Singh *et al.*. [22] (2013), kidney was the most affected organ (64.9%) followed by ureter (27.35%), urinary bladder (17.09%), prostate (3.4%) and epididymis (5.19%). In the study of 25 cases by Smita Chandra *et al.* [14] (2012) urinary bladder was the most affected in 7 cases (28%), followed by prostate in 6 cases (24%), kidney, epididymis, testes 3 cases each (12% each), ureter in 2 cases (8%) and scrotum in 1 case (4%). In the study of 31 cases by Orakwe. J.C *et al.*. [16] (2005) epididymis is the most affected organ in 25 cases (58.4%), followed by kidney in7 cases (16.3%), testis in 4 cases (9.3%), bladder in 3 cases (7%), ureter in 2 cases (4.7%), cord of testis in 1 case (2.3%) and prostate in 1 case (2.3%).

Table 7: Studies investigating the affected organs in GUTB

Organ of involvement	Singh *et al.*. [22] (2013)	Kulchavenya *et al.* [21] (2013)	Smita Chandra *et al.* [14] (2012)	Orakwe.J.C *et al.*. [16] (2005)	Current study
Kidney	64.9%	74.8%	12%	16.3%	45.61%
Ureter	27.35%	---	8%	4.7%	45.61%
Urinary bladder	17.09%	---	28%	7%	42.10%
Epididymis	5.19%	---	12%	58.4%	7.01%
Prostate	3.4%	---	24%	2.3%	---
Testis	---	---	12%	9.3%	----
Ovary	---	---	---	---	-----
Scrotum	---	---	4%	---	---
Cord of testis	---	---	---	2.3%	---

Radiology

Abnormalities on radiographic images can support the diagnosis of GUTB. Radiographic imaging, intravenous urography (IVU), ultrasonography and CT have been suggested to detect abnormalities at the site of disease in up to 95% of cases In this study CXR and ultrasonography have been done as a routine. IVU was done in 27 cases in our study and it detected abnormalities at the site of disease in 23 cases

(85.18%). In 4 cases IVU was normal who had TB cystitis. CT was done in 38 cases and all cases showed abnormalities at the site of disease. MRI was done in 10 cases who had

renal failure. Currently, at many centers, CT is replacing IVU as an imaging modality of choice in GUTB. Overall Radiological abnormalities suggestive of GUTB were found in 46 (80.7%) cases [23, 14]. In the study of khader *et al.* [12] Urography showed abnormalities in 80% of cases. The most frequent abnormality was a non-functioning kidney in 40.3%. Radiological abnormalities in genitourinary tuberculosis are reported in 63% to 95% of cases [23]. We found such evidence in 80.7% of our cases. The common radiological abnormalities seen were calcification, cortical scarring, calyceal destruction, nonvisualized kidney, ureteral stricture or irregularity and contracted bladder. This very high percentage may be due to late presentation of the cases.

Conclusion

The manifestations of genitourinary tuberculosis can be variable and causes a variety of clinical patterns that mimic other diseases. Most of the cases present with advanced disease and high index of suspicion is necessary for the early diagnosis of genitourinary tuberculosis. PCR presents an advance in the diagnosis of GUTB. Urinary PCR is the most sensitive indicator of all microbiological tests and in combination with radiological abnormalities provides much faster diagnosis of genitourinary tuberculosis. However, it is an elaborate test that requires meticulous care to avoid false-positive and false-negative results. Simultaneous testing of Urine for PCR, urine for MTB and urine for AFB in all patients yields higher positive results than each specific tests.

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Conflict of interest

The author declare that, they have no conflict of interest
Ethical clearance taken from Institutional ethical committee.

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