

# Utility of tissue Xpert-Mtb/Rif for the diagnosis of intestinal tuberculosis in patients with ileocolonic ulcers

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## Abstract

**Introduction:** Data on the use of Xpert Mtb/Rif for the diagnosis of intestinal tuberculosis is sparse. We report on the utility of Xpert Mtb/Rif testing for diagnosis of intestinal tuberculosis (ITB) in patients with ileocecal ulcers

**Methodology:** We performed a retrospective analysis of patients with ileocecal ulcers and suspected to have ITB and in whom testing of intestinal tissue for Xpert Mtb/Rif was performed. The patients were divided into two groups: those with a final diagnosis of intestinal tuberculosis and those with other diagnosis. These patients were compared for clinical features and presentation. The sensitivity, specificity, positive predictive value, and negative predictive value of Xpert Mtb/Rif for the diagnosis of ITB were calculated.

**Results:** Of the 40 patients studied, 23 were women and the mean age was  $32.92 \pm 12.78$  years. Abdominal pain was present in 33 (88.5%) patients and diarrhea in 12 (30%). A total of 25 patients had underlying ITB whereas 15 patients had other diagnoses (Crohn's disease, amebiasis, nonspecific ileitis, etc.). The sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of GeneXpert-Mtb/Rif was 32% (CI: 14.95–53.50%), 100% (78.2–100), 46.88% (40.27–53.59%), 100 & 57.50 (40.89–72.89%) respectively.

**Conclusion:** A positive GeneXpert-Mtb/Rif helps in the diagnosis of ITB, but the sensitivity is low.

**Keywords:** abdominal tuberculosis, polymerase chain reaction, Crohn's disease, colonoscopy, intestinal biopsy

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## Introduction

Extrapulmonary tuberculosis (EPTB) is reported in various studies to account for 15–20% of all cases of tuberculosis (TB).<sup>1</sup> Abdominal TB is an important form of EPTB and has been reported to account for 12.8% of all EPTB.<sup>2</sup> Various patterns of abdominal TB are peritoneal, luminal, lymph nodal, and visceral TB.<sup>3</sup> Luminal TB is further subdivided into intestinal, esophageal, and gastroduodenal involvement. Ileocecal region is the most common site of abdominal TB although any part of gastrointestinal tract (GIT) can be involved.<sup>3</sup> Intestinal tuberculosis (ITB)

may morphologically manifest as ulcerative, hypertrophic, or combined pattern. The ulcerative form presents more often with diarrhea and malabsorption, whereas the hypertrophic form presents with obstructive symptoms.<sup>3</sup>

Diagnosis of ITB by conventional methods is challenging because of the paucibacillary nature of the disease. In addition, the disease is known to closely mimic other intestinal pathologies especially Crohn's disease. Various criteria have been proposed for the diagnosis of abdominal TB, and have repeatedly emphasized the response to

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therapy as an important criterion because a positive diagnosis prior to initiation of therapy may not be possible even after endoscopic biopsies and microbiological investigations.<sup>3,4</sup>

The use of polymerase chain reaction (PCR)-based tests has been reported by many previous studies, but the availability of these test remains limited to a few centers.<sup>5,6</sup> The rapid diagnostic test GenXpert-Mtb/Rif is a cartridge-based nucleic acid amplification test (NAAT) for rapid diagnosis of TB and as well as simultaneously identifying the drug resistance (rifampicin resistance). This assay has a high diagnostic utility in pulmonary and lymph nodal TB and is being rolled out in the national TB programs. In a meta-analysis, the use of GenXpert-Mtb/Rif in EPTB has been reported to have a sensitivity of 77% and specificity of 97%.<sup>7</sup> However, the studies on the use of Xpert-Mtb/Rif in setting of ITB are limited to a few retrospective studies which have reported the positivity of this test to be 8–28% in patients with ITB.<sup>8,9</sup> However, none of the published reports describe the clinical utility of this test on intestinal tissue biopsy in patients with ileocecal ulcers. Therefore, we report findings from a retrospective cohort study where the patients with ileocecal ulcers who underwent Xpert-Mtb/Rif testing were included and the group with the final diagnosis of ITB was compared with those who had alternative diagnoses.

## Methodology

### *Setting and the patients*

This is a retrospective study of patients with ileocolonic ulcers who underwent colonoscopic examination and the intestinal tissue biopsy was evaluated for GeneXpert-Mtb/Rif for the diagnosis of ITB. From January to December 2018 we enrolled those patients who underwent colonoscopy and were found to have ileocolonic ulcers and who underwent the evaluation of tissue biopsy obtained at colonoscopy for Mycobacterium TB using GenXpert-Mtb/Rif.

The study was approved by the Institutional Ethics Committee vide letter number INT/IEC/2018/001834 and the need for informed consent waived in view of retrospective nature of study. In addition, all procedures were done in these patients only after a written informed consent.

### *Patients follow up*

The patients with abdominal TB are followed up in the Gut-TB clinic and the details are recorded in a prospective manner in the database. The clinical details, findings on history including details such as the presence of fever, abdominal pain, diarrhea, intestinal obstruction, loss of weight, appetite, etc. were retrieved from the records and entered into an excel sheet. The findings on clinical examination such as body weight, presence of pallor, lymphadenopathy, and lumps were also recorded. The colonoscopic findings including the presence of ulcer, polyps, nodules, strictures, and the site(s) of involvement were recorded. Other relevant findings such as HIV, Mantoux testing, chest X-ray were also recorded. The findings on histopathology such as the presence of granuloma, caseation necrosis, acid-fast bacilli (AFB) positivity, presence of changes of chronicity such as mucodepletion, crypt distortion, etc., and the findings on ultrasound, computed tomography, or repeat colonoscopy to document mucosal healing were noted.

Briefly, the patients with confirmed or probable ITB are started on standard four-drug daily anti-TB treatment (ATT) and followed up at least monthly for clinical response. We have a policy of repeating a colonoscopy at 2 or 6 months for documentation of early mucosal response (ulcer healing at 2 months) or end of therapy response (at 6 months).<sup>4,10</sup> Healing of ulcers is considered as evidence of TB as a diagnosis and absence of healing prompts workup for drug-resistant TB or alternative diagnosis.

### *Definitions*

The diagnosis of ITB was established using the criteria previously used by us as confirmed TB (microbiological positivity or caseating granulomas on histology) or probable TB (chronic inflammation, exclusion of diagnosis, and confirmation of mucosal healing on repeat colonoscopy).<sup>3</sup>

The study population was divided into two groups: ITB and other diagnosis (OTH) groups. The latter group included patients having other diagnoses such as Crohn's disease, other infectious disease, or any other lesion where GenXpert-Mtb/Rif was tested.

### Statistical analysis

Continuous variables were expressed as mean  $\pm$  standard deviation (SD). Categorical variables were expressed as percentages. The distribution of data was clarified using Kolmogorov–Smirnov test and in the case of a normal distribution the continuous variables were compared by Student's *t* test or nonparametric (Mann–Whitney *U*) test were used if the distribution was not normal. Categorical variables were compared by chi-squared test, and  $p < 0.05$  was considered to be significant. We also calculated sensitivity, specificity, positive predictive value, and negative predictive value of the Xpert/Mtb-Rif for diagnosis of ITB in patients with ileocecal ulcers.

### Results

The study included 40 consecutive patients with ileocecal ulcers. Of the 40 patients included, 23 (57.5%) were women. The mean age of study subjects was  $32.92 \pm 12.78$  years. The mean duration of symptoms was  $11 \pm 21.93$  months. Abdominal pain was present in 33 (82.5%) patients, loss of weight in 28 (70%), fever in 14 (35%), diarrhea in 12 (30%), episodes of intestinal obstruction in 7 (17.5%), and bleeding per rectum in 4 patients (10%). Chest roentgenogram was abnormal in 7 (17.5%) patients. The involvement as recorded on colonoscopy was reported as terminal ileal in 32 (80%), ileocecal valve in 24 (60%), cecum in 33 (82.5%), and rest of the colon in 18 (45%). Morphologically, the presence of mucosal ulcer (37 patients, 92.5%) was the most common finding, stricture was present in 10 (25%), and a few had polyps/nodular lesions 5 (12.5%). The findings on computer tomography included bowel thickening in 27 (67.5%) patients, lymphadenopathy in 19 ( $n = 28$ , 67.9%), ascites in 7 ( $n = 27$ , 17.5%) patients, and peritoneal thickening in 4 patients. Out of 40 patients, 4 (10%) underwent surgery for intestinal obstruction (Table 1).

On intestinal biopsy, granuloma was present in seven (17.5%), caseation in one patient, and AFB was positive on Ziehl-Neelsen stain in one patient. Crypt distortion was noted in 14 (35%). Erythrophagocytosis with trophozoites were seen in one patient and one had erythrophagocytosis alone in the OTH group. One patient had evidence of non-Hodgkin lymphoma on histology of the ulcers. Out of 40 patients, 25 were diagnosed as ITB, 10

as Crohn's disease, 2 as amoebic colitis, 2 as non-specific ileitis, and 1 as non-Hodgkin lymphoma.

None of the patients in the OTH group were Xpert positive whereas 8/25 patients in the ITB group were Xpert positive. Only one patient had rifampin resistance on Xpert-Mtb/Rif and was clinically found to deteriorate on the four-drug ATT with lack of resolution of ulcers. However, the patient improved with resolution of ulcers at a colonoscopy performed 2 months after starting DOTS-PLUS treatment. The sensitivity of GeneXpert-Mtb/Rif for diagnosis of ITB was 32% (95% confidence interval: 14.95–53.50%) while the specificity, negative predictive value, the positive predictive value, and accuracy were 100% (78.2–100), 46.88% (40.27–53.59%), 100, and 57.50 (40.89–72.89%), respectively.

Overall response to therapy (early mucosal response, i.e. mucosal healing at 2 months) was positive in 24 (96%) patients; that is, in all patients except the one with multi-drug-resistant TB. The granuloma positivity was present in 24% patients, AFB positivity in 4%, and Xpert Mtb/Rif in 32%. Of the eight patients who were Xpert Mtb/Rif positive, one each had granuloma positivity and AFB positivity. Therefore, the additional yield of Xpert Mtb/Rif over these tests was 24%.

### Discussion

ITB is a common presentation of EPTB that can closely mimic many abdominal diseases especially Crohn's disease.<sup>3</sup> In countries such as India, TB continues to be a major health concern for the clinicians and policy makers alike, but the prevalence of inflammatory bowel diseases is rising. In such a situation, discriminating ITB and Crohn's disease remains an important concern for gastroenterologists and clinicians. The clinical presentation, imaging findings, serological tests, endoscopic findings, and even histology may not discriminate these two entities and often clinicians resort to trial with ATT.<sup>3</sup> ATT trial is not without problems as it may unnecessarily increase the cost of therapy in Crohn's disease and exposes the patients to potentially hepatotoxic therapy. Therefore, better modalities are required to discriminate these two entities.

The introduction of Xpert-Mtb/Rif has provided clinicians a quick method to diagnose pulmonary TB and the test has also found utility in some forms

**Table 1.** Comparison between the clinical features and investigations of the two groups.

	<b>ITB (n = 25)</b>	<b>OTH (n = 15)</b>	<b>p value</b>
Clinical features			
<b>Duration of symptoms</b>	3 (3) <sup>a</sup>	12 (14) <sup>a</sup>	0.026
Pain	22 (25)	11 (15)	0.392 <sup>b</sup>
Diarrhea	6 (25)	6 (15)	0.311 <sup>b</sup>
Episodes of intestinal obstruction	4 (25)	3 (15)	1.0 <sup>b</sup>
Loss of weight	<b>22 (25)</b>	<b>6 (15)</b>	0.003 <sup>b</sup>
Fever	11 (25)	3 (15)	0.177 <sup>b</sup>
Bleeding per rectum	2 (25)	2 (15)	0.622 <sup>b</sup>
Investigations			
<b>Hemoglobin</b>	10.02 ± 1.66	11.2 ± 1.66	0.018 <sup>c</sup>
Total leukocyte count	7850 (1725) <sup>a</sup>	7350 (2375) <sup>a</sup>	0.415
Platelet	3.30 ± 1.49	3.73 ± 1.18	0.80 <sup>c</sup>
Bilirubin	0.6 (0.35) <sup>a</sup>	0.7 (0.44) <sup>a</sup>	0.636
Aspartate transaminase	26 (8) <sup>a</sup>	22 (8) <sup>a</sup>	0.062
Alanine transaminase	18 (7.6) <sup>a</sup>	21 (12.5) <sup>a</sup>	0.72
Alkaline phosphatase	146 (144) <sup>a</sup>	117 (45) <sup>a</sup>	0.263
Albumin	3.05 ± 0.958	3.20 ± 0.916	0.707 <sup>c</sup>
C-reactive protein	54 (59.6) <sup>a</sup>	30 (39.45) <sup>a</sup>	0.749
<b>Colonoscopy</b>			
Terminal ileum	21 (25)	11 (15)	0.444 <sup>b</sup>
Ileocecal valve	17 (25)	7 (15)	0.205 <sup>b</sup>
Cecum	23 (25)	10 (15)	0.163 <sup>b</sup>
Other parts of colon	12 (25)	6 (15)	0.747 <sup>b</sup>
Ulcer	23 (25)	14 (15)	1.0 <sup>b</sup>
Stricture	9 (25)	1 (15)	0.06 <sup>b</sup>
Polyp/nodule	5 (25)	0 (15)	0.137 <sup>b</sup>
<b>Histology</b>			
Granuloma	6 (25)	1 (15)	0.244 <sup>b</sup>
Caseation	1 (25)	0	1.00 <sup>b</sup>
Acid-fast bacilli	1 (25)	0	1.00 <sup>b</sup>
Crypt distortion	9 (25)	5 (10)	0.69 <sup>b</sup>
<sup>a</sup> Median value and applied nonparametric test. <sup>b</sup> Number of patients and chi-squared test applied. <sup>c</sup> Mean ± standard deviation and applied parametric test.			

of EPTB. The literature on the use of Xpert in diagnosis of ITB is limited to one retrospective study from India where the positivity was only amongst 3 out of the 37 patients who underwent the test and none had evidence of drug resistance.<sup>8</sup> Another study from Pakistan reported that 6 out of 21 patients with abdominal TB were positive for Xpert, however it is not clear if the peritoneal fluid or intestinal tissue or both were tested in this study.<sup>9</sup> The positivity of ITB in our set of patients was higher and this was even though the AFB positivity was low in our patients. This may be related to the fact that we sent two pieces of tissue for the Xpert testing. In addition, one of our patients also had positive Xpert for rifampin resistance and indeed did not have clinical or mucosal response to standard antitubercular therapy. The patients had an excellent clinical response and mucosal healing 2 months after initiation of DOTS-PLUS therapy. These findings suggest that testing with Xpert-Mtb/Rif in patients with suspected ITB may not only help in diagnosis but also detect drug-resistant TB. Our study also suggests that although the sensitivity is low, the specificity and positive predictive value for Xpert Mtb/Rif for diagnosis of ITB are excellent. The study has some limitations including the small number of included patients and the fact that TB culture was not routinely done.

These results, coupled with the fact that Xpert Mtb/Rif has been rolled out in the program, suggest that the use of Xpert for diagnosis of ITB in patients with ileocecal ulcers should be routinely considered especially because the results, as against culture testing, are available rapidly. Although the negative test may not exclude ITB but a positive test confirms the diagnosis and may suggest whether drug resistance is present or not.

### Conflict of interest statement

The authors declare that there is no conflict of interest.

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