

# Making a Positive Diagnosis of Intestinal Tuberculosis with the Aid of New Biologic and Histologic Features: How Far Have We Reached?

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## Keywords

Intestinal tuberculosis · Mycobacteria Growth Indicator Tube culture · Colonoscopy

## Abstract

**Background:** The diagnosis of intestinal tuberculosis (TB) and its differentiation from Crohn's disease (CD) remain a challenge. We review here in detail the various methods for the diagnosis of intestinal TB. **Summary:** Colonoscopy findings in intestinal TB are useful and suggestive; histopathology of colonoscopic biopsies is contributory but rarely confirmatory. Increasing the number of colonoscopic biopsies increases the histological yield. Recent culture methods that have improved the yield for TB offer hope. Mycobacteria Growth Indicator Tube (MGIT) culture is now the standard of care as its yield is superior to that of the traditional Lowenstein-Jensen medium. Increasing the number of colonoscopic biopsy samples for MGIT culture can increase the yield. The culture and histology are complimentary. Even then a significant proportion of patients do not have a positive diagnosis of intestinal TB. Scoring systems have been developed with a sensitivity and specificity of 90 and 60%, respectively, but their utility in routine practice is yet to be established. Similarly, the ratio of visceral fat to total fat is helpful in differentiating CD from intestinal TB. Polymerase

chain reaction has been used but its value seems uncertain. Gene Xpert<sup>®</sup> in an emerging technique that has been found to be useful in the diagnosis of pulmonary TB, and its utility in intestinal TB needs to be looked at. Newer technologies like TB-LAMP (loop-mediated isothermal amplification) need to be assessed in clinical studies. **Key Message:** Optimization of the present diagnostic tools (taking an adequate number of biopsies for histology and culture) and study of newer techniques to learn their actual utility seems to be the way forward.

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## Introduction

Worldwide, approximately 9.6 million people were estimated to have been afflicted with tuberculosis (TB) in 2014, including 5.4 million men, 3.2 million women, and 1.0 million children [1]. Geographically, the burden of TB is highest in Asia and Africa. India and China together account for almost 40% of the world's cases. In these 2 countries, less than 1 in 10 cases has multidrug-resistant TB, but a scale-up is expected in the next 3 years [2]. The proportion of patients with extrapulmonary TB is 8–13%, and among these abdominal TB accounts for 7% of the patients [3].

**Table 1.** Histology findings in intestinal TB

Study	Patients with TB, <i>n</i>	Granuloma, %	Caseation, %	Nonspecific features, %
Vij et al. [9]	37	67	13	33
Shah et al. [10]	50	74	18	20
Pulimood et al. [11]	61	46	18	
Kirsch et al. [12]	18	78	22	22
Amarapurkar et al. [13]	26	57	34	38

The numbers are not mutually exclusive.

It is generally believed that the incidence of Crohn's disease (CD) is increasing in countries afflicted by TB [4], and differentiating intestinal TB from CD is often a challenge [5]. Isolation of acid-fast bacilli (AFB) is a vital step in the diagnosis of intestinal TB and its differentiation from CD; a positive culture also enables drug sensitivity testing and thus the diagnosis of multidrug-resistant TB.

Digestive tract sarcoidosis can very rarely mimic TB or CD. The most common site of involvement is the stomach, followed by the colon. Patients present with abdominal pain, weight loss, nausea/vomiting, diarrhea, and digestive bleeding. Differentiating digestive tract sarcoidosis from CD and intestinal TB can be difficult. Thoracic adenopathy, other systemic features, and a negative TB culture may lead to suspicion of this relatively rare disease. However, histological examination of large specimens may yield the final diagnosis [6–8].

### Histological Diagnosis of Intestinal TB

The availability of colonoscopic biopsy has significantly reduced the need for surgical/laparoscopic access for tissue. Histology is often not definitive for a diagnosis of TB, and culture remains the gold standard.

Histological features of TB include granulomas with caseating necrosis, conglomerate epithelioid histiocytes, and disproportionate submucosal inflammation. As shown in Table 1, the classical histological features are seen in only 13–33% of patients; the presence of granulomas in a clinically suggestive setting helps to reach the diagnosis in 57–74% of the patients [9–13].

A larger number of biopsy samples available for histology is naturally expected to increase the diagnostic yield for TB; however, this comes at the cost of more time for biopsies and processing. Various authors have recommended 4–10 biopsies. Yönel and Hamzaoğlu [14], in a

review, recommended at least 8 colonoscopic biopsies for a satisfactory histological evaluation, based on data given in various studies.

### AFB Culture in Intestinal TB

There are 3 types of AFB culture medium, i.e., egg-based (the traditional Lowenstein-Jensen [LJ] medium), agar-based (e.g., Middlebrook 7H10 or 7H11), and liquid (Middlebrook 7H12 and other commercially available broths) media.

Newer methods include the radiometric BACTEC 460 system, the MGIT BACTEC 960 system, and the EPS II system. The BACTEC system, developed by Becton Dickinson (New York, NY, USA), is based on generation of radioactive carbon dioxide from substrate palmitic acid [15]. The Mycobacteria Growth Indicator Tube (MGIT) system (also developed by Becton Dickinson) is based on a nonradioactive method using fluorochromes for detection of growth and drug screening. This system helps in early detection (7–12 days) of mycobacterial growth and has been reported to be useful for drug susceptibility testing [16].

The MGIT system has several benefits besides being radiation free. Full automation eliminates loading and unloading of tubes and thus minimizes the risk of bottle breakage; CO<sub>2</sub> tanks are not required; the noninvasive monitoring of cultures eliminates the possibility of cross-contamination; the use of screw caps on the tubes eliminates the need for use of needles and thus the risk of inadvertent needle pricks [17–19]. Hence, the MGIT system is today the preferred method of isolation of the TB organism.

The yield of AFB culture on LJ medium is poor, ranging from 6 to 48% [9, 10]. Morgan et al. [20] and Bhargava et al. [21] compared the bacteneccin (BACTEC) system with Middlebrook 7H100 and LJ media (Table 2).

**Table 2.** Comparison of traditional culture methods and the MGIT BACTEC 960 system

Study	Ratio of positive samples/ total samples	LJ medium		Middlebrook 7H10		MGIT BACTEC 960	
		positive samples, %	recovery time, days	positive samples, %	recovery time, days	positive samples, %	recovery time, days
Morgan et al. [20] <sup>a</sup>	71/2,165	44	26	39	26	51	13
Bhargava et al. [21] <sup>b</sup>	58/100	53	35	39	42	53	20

<sup>a</sup> Included all smear-negative pulmonary and extrapulmonary samples excluding CSF and urine. <sup>b</sup> Included 73 pulmonary and 27 extrapulmonary samples.

**Table 3.** AFB culture positivity on LJ medium and the BACTEC method in intestinal TB

Study	Sample size, <i>n</i>	Source	Culture positivity, %	Method
Shah et al. [10]	50	Colonoscopy	6	LJ medium
Kirsch et al. [12]	18	Colonoscopy	11	BACTEC
Shah et al. [22]	28	Colonoscopy + surgery	48	LJ medium
			76	BACTEC
Samant et al. [23]	62	Colonoscopy	50.8	BACTEC

They reported the highest AFB culture yield and the fastest growth on the MGIT 960 system.

Studies based on surgical specimens have shown higher TB culture rates. Shah et al. [22] studied 9 patients with surgical biopsies and 18 with colonoscopic biopsies. The BACTEC method was superior, with 76% positivity as compared to 48% on LJ medium. In this study surgical specimens increased the AFB culture positivity.

### Number of Biopsies and Increasing Yield

Table 3 shows the AFB culture positivity in patients with intestinal TB. Earlier studies had a much lower culture positivity rate [22]. There has been a recent gradual improvement in the yield from colonoscopic biopsies to nearly 51% [23]. As mentioned earlier, the yield of histopathology can be increased by taking 8 biopsies. Similarly, 8 biopsies can increase the yield of AFB culture as compared to 4 biopsies. In an earlier study, we examined 190 patients suspected to have intestinal TB, over a period of 2 years, and 70 patients had confirmed TB based on histology and/or AFB culture. The study revealed that taking 8 biopsies increased the diagnostic yield by 11.4% as compared to 4 biopsies [24].

### Combining Histology and AFB Culture for Diagnosis of Intestinal TB

Given the limitations of histology and AFB culture, combining the two methods may improve the diagnostic yield. This will reduce the number of patients who receive empiric anti-TB treatment. The combined yield has improved from 75% in earlier studies to 92% in a recent study (Table 4, footnote d) [9, 10, 13, 22, 23, 25].

### Scoring for Differentiation between Intestinal TB and CD

Makharia et al. [26] devised a score on the basis of regression coefficients of the final multivariate logistic model, which varied from 0.3 to 9.3. Higher scores predicted a greater likelihood of intestinal TB. With the cut-off at 5.1, the area under ROC in the validation data set was 89.2% (95% CI 0.79–0.99) and the sensitivity and specificity were 90% (95% CI 66.9–98.2) and 60% (95% CI 36.4–80.0), respectively. The low specificity restricts the positive diagnosis.

**Table 4.** Diagnostic yield of histology and AFB culture in intestinal TB

Study <sup>d</sup>	Patients with ileocolonic TB, <i>n</i>	Histology, <i>n</i> (%)	AFB culture positivity, <i>n</i> (%)	Culture method	Combined diagnostic yield, %
Vij et al. [9]	28	21 (75)	13 (46)	LJ medium	75 <sup>a</sup>
Amarapurkar et al. [13]	26	13 (50)	6 (23)	BACTEC	Not commented <sup>b</sup>
Shah et al. [10]	50	40 (80)	3 (6)	LJ medium	80
Leung et al. [25]	23	3 (13)	17 (73)	BACTEC	82
Krisch et al. [12]	18	14 (78)	14 (78)	BACTEC	78
Samant et al. [23]	61	48 (78.6)	31 (50.8)	BACTEC	91.8
Shah et al. [22] <sup>c</sup>	28	NA	48	LJ medium	NA
			76	BACTEC	

NA, not available. <sup>a</sup> Included all gastrointestinal TB cases. <sup>b</sup> Included parameters like clinical score and TB PCR. <sup>c</sup> Included only histology-positive cases. <sup>d</sup> In these studies the gold standards for the diagnosis of intestinal TB were: culture positivity and, in presence of convincing clinical features, imaging evidence and histological features with a positive response to treatment documented by repeat imaging or colonoscopy.

**Table 5.** Sensitivity and specificity of TB PCR in intestinal TB

Study	Type of sample	Sensitivity, %	Specificity, %
Amarapurkar et al. [13]	Paraffin-embedded biopsy specimens	21.6	95
Hillemann et al. [29]	Paraffin-embedded biopsy specimens	66	100
Pulimood et al. [30]	Deparaffinized biopsy specimens (in situ PCR)	30	95
Gan et al. [31]	Paraffin-embedded biopsy specimens	64.1	100

### Visceral Fat/Subcutaneous Fat Ratio on CT Scan

Two recent retrospective studies have examined the ratio of visceral fat to subcutaneous fat in patients with CD and intestinal TB. Similarly, the ratio of visceral fat to total fat has also been studied. The ratio of visceral fat to subcutaneous fat and the ratio of visceral fat to total fat are higher in CD as compared to intestinal TB. For a VF/TF cut-off value of 0.46, the sensitivity and specificity for the diagnosis of CD were 42.1 and 93.3% respectively, with positive and negative predictive values of 88.9 and 56.0%, respectively [27]. A cut-off of 0.63 for the VF/SC ratio had a high sensitivity of 82% and a specificity of 81% in differentiating CD and intestinal TB [28].

### Newer Diagnostic Modalities

#### TB Polymerase Chain Reaction Methods

Various polymerase chain reaction (PCR) methods have been developed for the detection of specific sequenc-

es of *Mycobacterium tuberculosis* and other mycobacteria. These assays may target DNA or rRNA. Three main types of PCR techniques are available, i.e., DNA targeting probe, rRNA targeting probe, and gene amplification assay [28]. Although the specificity of PCR assay is very high (Table 5), its low sensitivity has limited its use in clinical practice [13, 29, 30, 31]. The small quantity of tissue available in mucosal biopsy specimens and the limited number of sections used for DNA extraction may limit the copy numbers of *M. tuberculosis* DNA; hence the low sensitivity.

#### Gene Xpert<sup>®</sup> Assay

The Xpert MTB/RIF (rifampicin) assay is a fully automated real-time PCR-based test designed for rapid and simultaneous detection of *M. tuberculosis* and mutations associated with rifampicin resistance, and the result is available within 2 h [32, 33]. The test is expensive but it is marketed as a point-of-care test and requires virtually no training or laboratory infrastructure. Pimkina et al. [34] conducted a study on sputum and bronchoalveolar lavage specimens and showed that the sensitivity of the Gene

Xpert assay is nearly 100% when AFB are detected on a smear. Smear-negative but culture-positive specimens had a sensitivity of 85%. For smear- and culture-negative specimens, the sensitivity of the assay was only 8%. Thus, the advantage of the Gene Xpert assay is achievement of a rapid diagnosis at a point of care and additional information about drug resistance, rather than an additional yield. An Indian study [35] included pulmonary ( $n = 384$ ) and extrapulmonary ( $n = 761$ ) samples. Among the latter, the sensitivity of the Gene Xpert assay was 88% and its specificity was 91%. Kumar et al. [36] found that the sensitivity, the specificity, the positive predictive value, and the negative predictive value of the Gene Xpert assay were 8.1, 100, 100, and 64.2%, respectively, in intestinal TB cases.

#### *Loop-Mediated Isothermal Amplification Test for TB*

This method is fast, results can be detected by the naked eye, and it does not require expensive equipment. Current TB-LAMP (loop-mediated isothermal amplification) assays are based on amplification of MTBC genomic DNA targeting the *gyrB* and *IS6110* genes. A study done by Kumar et al. [37] on 118 clinical samples (41 pulmonary samples [sputum,  $n = 29$ ; bronchoalveolar lavage,  $n = 7$ ; and gastric aspirate,  $n = 5$ ] and 77 extrapulmonary samples [CSF,  $n = 28$ ; pus,  $n = 11$ ; pleural fluid,  $n = 15$ ; ascitic fluid,  $n = 2$ ; lymph node aspirate,  $n = 7$ ; urine,  $n = 5$ ; abscess pus,  $n = 3$ ; and other body fluids,  $n = 6$ ]). LAMP showed a higher detection rate (52.5%) as compared to mPCR (multiplex PCR) (44%) and culture (30.5%). On culture-positive and mPCR-positive samples, the sensitivity of LAMP was 100% and its specificity was 96.1%. Similarly, Bojang et al. [38] reported sensitivities and specificities of 98.6 and 99% for TB-LAMP, 91.1 and 100% for MGIT culture, and 99.1 and 96% for Gene Xpert for the diagnosis of TB. These new studies have not significantly improved on sensitivity or specificity for the diagnosis of TB. However, these studies are useful for early diagnosis of *M. tuberculosis* and identification of drug-resistant strains.

#### *Proteomic Profiling*

The differently expressed protein peaks analyzed by serum proteome with weak cationic magnetic beads combined with the matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF-MS) technique can effectively distinguish CD patients from healthy controls (HC), intestinal TB patients from HC, and CD patients from Intestinal TB patients. Zhang et al. [39] conducted a study on 30 CD patients, 21 intestinal TB patients, and 30 HC and concluded that:

- the diagnostic model between CD patients and HC consisting of 4 protein peaks (M/Z 4964, 3029, 2833, and 2900) had a sensitivity and specificity of 96%;
- the diagnostic model between intestinal TB patients and HC comprising 4 protein peaks (M/Z 3030, 2105, 2545, and 4210) had a sensitivity and specificity of 93 and 95%, respectively; and
- the differential diagnostic model between CD patients and intestinal TB patients comprising 3 protein peaks (M/Z 4267, 4223, 1541 and) had a sensitivity and specificity of 76 and 80%, respectively [39].

Similarly, protein expression in macroscopically affected mucosa is different in CD and Intestinal TB. Rukmangadachar et al. [40] identified 63 proteins differentially expressed in colonic mucosa of patients with CD and intestinal TB and 6 proteins used for validation employing immunohistochemistry in a larger cohort of patients. However, multiple large-scale studies will be required for further validation of these findings [40].

In summary, a positive diagnosis of intestinal TB remains a challenge due to limitations in histology and culture, which are the presently relied-upon methods for the diagnosis of intestinal TB. With an increasing prevalence of CD in countries like India, differentiating this disease from TB is increasingly important. The refinement in culture has improved the yield of culture to about 50%. The combination of histology and culture is complimentary. Optimization of the present diagnostic tools (taking an adequate number of biopsies for histology and culture) and study of newer techniques to learn their actual utility seems to be the way forward.

#### **Statement of Ethics**

Since this is a review, it has not involved any patients/animals or any intervention. This article has not been subjected to institutional review board review.

#### **Disclosure Statement**

None of the authors have any conflict of interest.

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