

# Colitis Tuberculosis

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## ABSTRACT

*Tuberculosis (TB) is a significant public health problem worldwide. Indonesia is a country with the third highest prevalence of TB in the world after China and India. TB infection can attack all organs of the human body. TB in digestive system is one of the extrapulmonary TB manifestations and comprises of 3-16% of all extrapulmonary TB cases. This type of TB may affect digestive system, peritoneum, mesentery lymphatic glands, liver, and spleen. Digestive system is affected in 66-75% of patients with abdominal TB. The ileocaecal region is most commonly affected. The manifestation of abdominal TB is not specific. Precise diagnostic approach and supporting results are needed to determine final diagnosis. However, there is no single examination adequate enough to diagnose abdominal TB. If the diagnosis can be established early, this disease could then be managed with conventional anti-TB drugs. Treatment for both 6-9 months period and 18-24 months period has been proven effective in management of extrapulmonary TB.*

*In countries with high abdominal TB prevalence, initiation of anti-TB therapy is allowed if there are the clinical features present. Diagnosis can be determined when the patient has therapeutic response against the anti-TB treatment.*

**Keywords:** tuberculosis, colitis, extrapulmonary, antituberculosis drugs

## INTRODUCTION

Tuberculosis (TB) is an important public health problem worldwide. Indonesia is a country with the third highest prevalence of TB in the world, right after China and India. Based on the 1985 Household Health Survey and the 2001 National Health Survey, TB is positioned as the third highest cause of death in Indonesia.<sup>1,2,3</sup>

TB in digestive system is one of the manifestation of extrapulmonary TB and comprises of 3-16% of all extrapulmonary TB cases. The digestive system is involved in 66-75% of patients with abdominal TB. The gastrointestinal region that most commonly affected is the ileocaecal region.<sup>3,4</sup> TB in digestive system also has unclear or hidden clinical features with

no specific laboratory results or radiologic features. Clinical evaluation is required for early diagnosis and correct treatment.<sup>4,5,6</sup> Treatment with the standard regimen of drugs for TB in the digestive system is quite effective. Steroid as an additional treatment remains arguable.<sup>1,6,7,8</sup>

## MORPHOLOGY AND STRUCTURE OF THE BACTERIA

TB is a disease caused by the infection of *Mycobacterium tuberculosis* (*M. tuberculosis*) complex.<sup>3</sup> *M. tuberculosis* has the shape of straight or slightly curved rod, no spores, no capsule, and is 0.3–0.6 µm in width and 1–4 µm in length. Bacterial wall is very complex, comprising of relatively high fat layers (60%) which main components are mycolic acids, complex waxes, dimycolic trephalose called cord factor and mycobacterial sulfolipids which plays a role in virulence. Other components of the bacterial cell wall are polysaccharides, such as arabinogalactan and arabinomannan. The complex structure of the cell wall allows the bacteria to be acid-fast in nature.<sup>1,2,3</sup>

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## TRANSMISSION

The process of *M. tuberculosis* infection is commonly transmitted by inhalation leading to pulmonary TB, which is the most common clinical manifestation compared to other organs. The transmission of this disease is mostly achieved by inhaling bacilli which contains droplet nuclei specifically from pulmonary TB patients with productive cough or hemoptoe which contains acid fast bacilli (AFB). Infections caused by *Mycobacterium bovis* might be transmitted through milk which is not adequately sterilized or has been contaminated.<sup>1,2</sup>

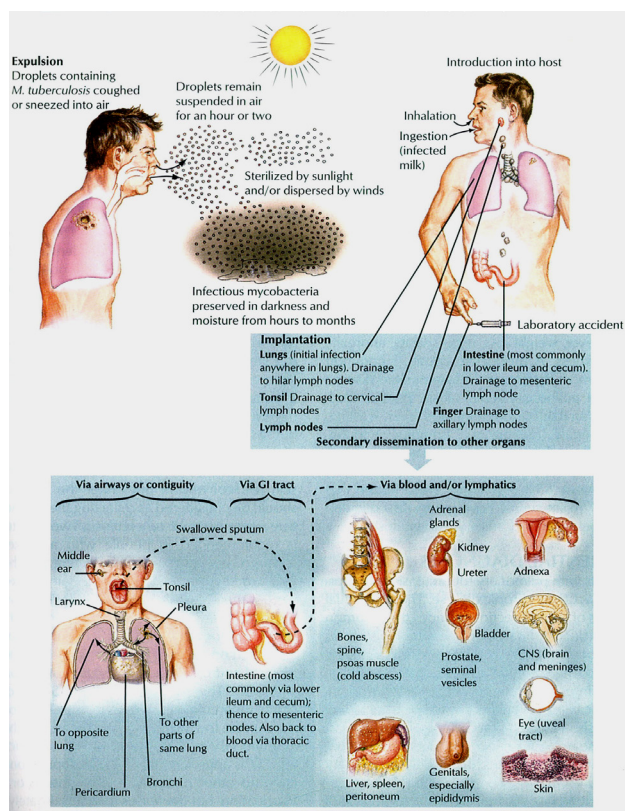


Figure 1. Dissemination of tuberculosis<sup>2</sup>

## PATHOGENESIS OF TUBERCULOSIS

### Primary Tuberculosis

TB bacteria which enter respiratory tract will nest in lung tissue to form a pneumonic nest called primary nest or primary complex or Ghon's focus. The primary complex may emerge in any parts of the lungs, unlike the reactivation focus. From the primary complex, lymphatic vessels' inflammation towards the hilus (local lymphangitis) shall occur. The inflammation is followed by the enlargement of hilar lymph nodes (regional lymphadenitis). Primary complex, together with local lymphangitis and regional lymphadenitis, is known as the primary complex of Ranke.<sup>1,2,3</sup>

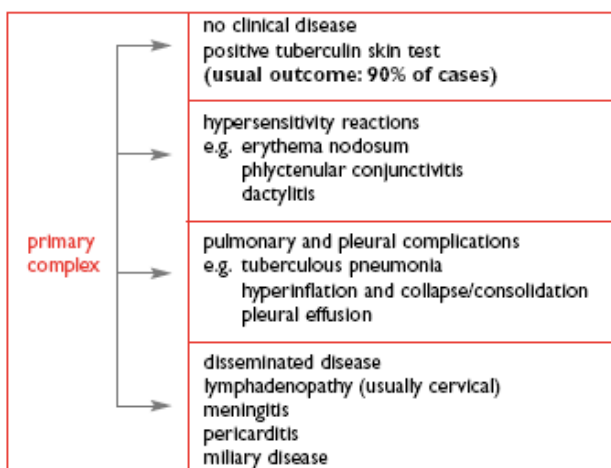


Figure 2. Outcomes of primary infection<sup>9</sup>

### Secondary Tuberculosis (Post Primary Tuberculosis)

Dormant microorganisms in primary TB will emerge years later as endogenous infection in adults, usually occurring in the age of 15-40 years. The majority of reinfection is mounting up to 90%. Post primary TB starts with a complex commonly located in posterior-apical segment of either superior or inferior lobes. Its invasion is directed to the parenchyma of lungs. This early complex is at first shaped as a small pneumonia complex. Within 3-10 weeks, it will then become a tubercle, a granuloma which consists of histiocytes and Datia Langhans cells (giant cells with multiple nuclei) which are surrounded with lymphocytes and various connective tissues. Depending on the number of agents, virulence, and patient's immunity, this pneumonic complex will then follow a certain pathway: gets reabsorbed back and heals without leaving any marks, spreads and healing process begins quickly along with the forming of fibrotic tissue, or pneumonic complex spreads widely to form caseous tissue. Cavity will emerge as the caseous tissue gets coughed out. The cavity will then spread and create new pneumonic affect. This pneumonic complex shall follow one pattern of pathways as mentioned above, get condensed and encapsulates itself and known as tuberculoma. It is clear and heals to produce what is called open healed cavity, or heals by encapsulating itself and finally shrink down.<sup>1,2,3</sup>

### DEFINITION OF COLITIS TUBERCULOSIS

Colitis is an acute or chronic inflammation in colon which, based on the etiology, can be classified as follows:<sup>3,4,5</sup> (1) Infective colitis, such as: shigellosis, colitis TB, amebic colitis, pseudomembrane colitis, colitis of other viral/bacterial/parasite etiologies; (2) Non-infective colitis, such as: ulcerative colitis, Crohn's disease, radiative colitis, non-specific colitis.

**Table 1. Post primary tuberculosis<sup>9</sup>**

Pulmonary tuberculosis	Extrapulmonary tuberculosis	
	Common	Less common
Cavities	Pleural effusion	Empyema
Upper lobe infiltrates	Lymphadenopathy (usually cervical)	Male genital tract (epididymitis, orchitis)
Fibrosis	Central nervous system (meningitis, cerebral tuberculoma)	Female genital tract (tubo-ovarian, endometrium)
Progressive pneumonia	Pericarditis (effusion/constrictive)	Kidney
Endobronchial	Gastrointestinal (ileocaecal, peritoneal)	Adrenal gland
	Spine, other bone and joint	Skin (lupus vulgaris, tuberculids, miliary)

TB in the digestive system is one of the manifestations of extrapulmonary TB and comprises of 3-16% of all extrapulmonary TB cases. This type of TB can affect the digestive system, peritoneum, mesenteric lymph nodes, liver, as well as spleen. The digestive system is affected in 66-75% of patients with abdominal TB. Guts and peritoneum can be infected through mesenteric lymph nodes, infected tuba falopii, direct spread from an infected organ, and hematogenous spread. Direct infection from the wall of the guts is highly possible after drinking unpasteurized milk or swallowing a large number of bacilli from the pulmonary cavity. Reactivation from the body within few years of time after hematogenous spread is highly possible.<sup>7,8</sup>

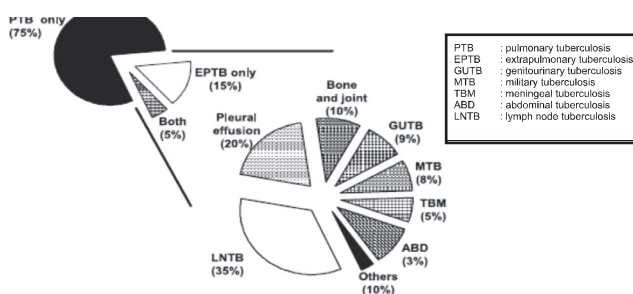


Figure 3. Distribution of tuberculosis cases by anatomical site in HIV negative patients<sup>10</sup>

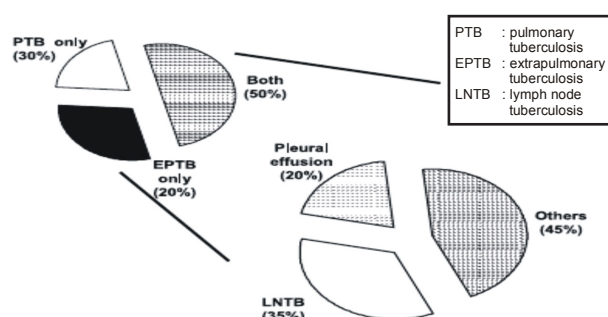


Figure 4. Distribution of tuberculosis cases by anatomical site in HIV positive patients<sup>10</sup>

In colitis TB, caecum and ascending colon are two areas most frequently affected, followed by transverse colon and descending colon. Based on several references, 6-90% of patients with pulmonary TB

have enteric involvement. This big interval is caused by the severity of pulmonary TB, where the degree of severity of pulmonary TB is directly proportional to the incidence of concurrent enteric involvement.<sup>7,8</sup>

**Table 2. Anatomic distribution of tuberculosis of the intestine (from clinical and necropsy series)<sup>8</sup>**

Site	Cases (%)
Duodenum	2-3
Jejunum	7-25
Ileum	70-80
Ileocecal area	55-85
Appendix	5-25
Colon	25-50
Rectum	5-10
Anal canal	0-4

On the other side, 7-75% of patients with enteritis TB have no history of concurrent pulmonary TB based on various reports in Canada, USA, and England. Studies in India reported that 60-75% of patients with enteritis TB have no association with active pulmonary TB, 0-20% have association with active pulmonary TB, and 5-40% have association with inactive pulmonary TB.<sup>7,8,11</sup>

## **PATHOGENESIS OF COLITIS TUBERCULOSIS**

The pathogenesis of abdominal TB can be divided into 4 mechanisms are swallowing infected sputum, hematogenous spread from an active pulmonary process or miliary TB, consuming contaminated milk or food and direct spread from the adjacent organs. Infection may occur primarily in the gastrointestinal tract or secondary from other focuses in the body.<sup>7,8,11</sup>

In the case of ingested tubercle bacilli, intestinal TB might be caused by consuming contaminated food and milk. Secondary infection can happen due to swallowing infectious sputum in patients with pulmonary or laryngeal TB. After ingestion, bacteria shall pass the stomach and head to the small intestine. The lipid capsule protects bacteria from digestion process such as the stomach acid secretions. In the intestines, germination process takes place in



areas containing many lymphoid tissues, excessively static in physiology, areas with high rate of water and electrolyte absorption, as well as areas with minimal digestive activity.<sup>1,7,8,11</sup>

While the hematogenous spread from extraintestinal focuses of infection involves spreading through blood which can occur in primary phase of pulmonary TB and in miliary TB. In these conditions, early lesions are found in submucosa area, with normal mucosa appearance.<sup>8,11</sup>

The most frequently affected location is the ileocaecal region. The affinity of TB bacilli in this region might be due to the presence of many lymphoid tissues with relatively slower stream. Microorganisms penetrate the mucosa to settle in submucosal lymphoid tissues, where they would start inflammatory reactions which lead to the emergence of lymphangitis, endarteritis, granuloma, caseous necrosis, mucosal ulcerations, and fibrotic tissue.<sup>3,8,11</sup>

Macroscopic feature of intestinal lesions can be categorized as follows: ulcerative (60%), hypertrophic (10%), and ulcerous-hypertrophic (30%). The ulcerous-hypertrophic feature is most frequently found in ileocaecal TB in comparison to the TB affecting other segments of gastrointestinal tracts.<sup>8,11,12</sup>

## CLINICAL MANIFESTATIONS

The signs and symptoms are blurry and not specific. The clinical manifestations might be acute, chronic, or acute in chronic process. As a result, the diagnosis of ileocaecal TB is hard to establish and requires high clinical suspicion rate, especially in the high-risk group.<sup>1,7,8,11,12,13</sup>

In literatures, it is mentioned that TB of the digestive system occurs more frequently in young adult. Two thirds of the patients are 21-40 years old and in several studies it was shown that the incidence in women is higher than that in men (2 : 1).<sup>3,4,14</sup>

In a study conducted by Khan et al the average age was  $33 \pm 15$  years old with 59% of the patients were women. The most frequent symptoms found subsequently were abdominal pain, fever, night sweat, weight loss, nausea, vomiting, ascites, constipation, and diarrhea. Subacute and acute intestinal obstruction was found in 13% and 11% of all patients, respectively. The length of time the symptoms had been experienced before the patients received their medication for the first time was  $265 \pm 150$  days. History of previous TB treatment was found in 6,2% of patients and a history of TB among family members was found in 2.9% of patients.<sup>7,14,15</sup>

In history of illness, the symptoms found were abdominal pain, night sweats, weight loss, loss of appetite, nausea, vomiting, and chronic diarrhea. Most patients have constitutional symptoms

such as fever (40-70%), pain (80-95%), diarrhea (11-20%), constipation, alteration between constipation and diarrhea, weight loss (40-90%), anorexia and weakness. Unspecific chronic abdominal pain was the chief complaint in 80 to 90 percent of all patients. Pain might be colic or continuous if the mesenteric lymph nodes were involved.<sup>1,5,6</sup>

Mass in lower right quadrant was palpable in 25-50% of all patients. Intestinal obstruction and colon perforation were reported. Abdominal distention due to ascites was various between 10-65%. The presence of ascites could help to differentiate ileocaecal TB and Crohn's disease considering that ascites is rarely found in Crohn's disease. The proportion of the occurrence of this case along with abdominal TB is varied between 30-40%.<sup>7,8,14,16</sup>

**Table 3. Symptoms and signs of tuberculosis<sup>17</sup>**

Symptoms	n (%)	Signs	n (%)
Weight loss	49 (57)	Fever	40 (46.5)
Abdominal pain	43 (50)	Ascites	23 (27)
Pyrexia of unknown origin	36 (42)	Abdominal tenderness	23 (27)
Abdominal distension	19 (22)	Abdominal mass	10 (11.5)
Vomiting	13 (15)	Peritonitis	3 (3.5)
Night sweats	7 (8)	Acute bowel obstruction	2 (2)
Anorexia	7 (8)	Jaundice	1 (1)
Cough	3 (3.5)	Fistula-in-ano	1 (1)
Dysphagia	2 (2)	Perianal mass	1 (1)
Shortness of breath	1 (1)	Post-cholecystectomy	1 (1)
PR bleed + mass at anal margin	1 (1)	Neck mass	1 (1)
Fistula-in-ano	1 (1)		

In laboratory examination, routine laboratory result can indicate mild anemia and increased erythrocyte sedimentary rate in 50-80% of patients. Leukocyte count is usually within normal range. Positive tuberculin test in most of the patients with intestinal TB has limited diagnostic value since it cannot differ between active disease and previous sensitization due to contact or vaccination. Furthermore, purified protein derivative (PPD) skin test might give negative result in immune-compromised patients.<sup>12,13,14,16</sup>

The examination of acid-fast bacilli (AFB) of sputum, stools, and tissue AFB as well as the result of tissue AFB culture often give negative results. In a study conducted by Wells, Northoven and Howard, positive result of sputum and tissue AFB test were achieved only in less than 50% of all cases. A Canadian study, AFB culture from tissue specimen collected through surgical procedures only gives positive results in 8 out of 17 patients with abdominal TB and direct tissue-AFB examination gives positive results in

5 out of 17 patients. Khan et al showed positive results for mycobacterium tissue culture only in 7% of patients with abdominal TB and the sensitivity of acid-fast bacilli examination was 24.3%.<sup>8,11,12,14,16</sup>

Radiology findings are not specific. Patients' chest X-ray often shows no abnormalities. This condition is not a wonder, considering less than 50% of patients show pulmonary abnormalities. The image of specific process in roentgen photo leads to the diagnosis, but it was also mentioned that a normal chest X-ray does not exclude abnormalities. Sharma et al found coincidence with pulmonary TB as much as 46%.<sup>12,13,14,16</sup>

**Table 4. Diagnostic yield of various investigations in patients with abdominal tuberculosis<sup>17</sup>**

Investigations	n (patients in which investigations performed)	Yield of diagnostic test n/%
Barium meal and follow through	70	58/83
Barium enema	34	15/44
Ultra sound	93	82/88
CT scan abdomen	35	28/80
Histopathology of	35	35/100
Histopathology of surgical specimen	35	29/83
Histopathology of colonoscopic biopsy	28	14/50
Histopathology of ultrasound and CT guided biopsy	5	5/100
Histopathology of upper GI endoscopic biopsy	10	4/40
Acid fast bacilli culture	87	6/7

Barium enema and follow-through can show mucosal ulceration and stricture, caecal deformity and gaping, or incompetent ileocaecal valve. CT is an imaging modality which helps in judging intraluminal and extraluminal pathology as well as the distribution of the disease.<sup>12,14,16,15,18</sup>

Eventhough colonoscopy nowadays has largely replaced the role of past radiologic examination, double-contrast barium enema examination can provide a more detailed information on mucosal pattern and early images of intestinal TB. With a better understanding of early radiologic features of colitis TB, an earlier diagnosis using double-contrast barium enema is made possible.<sup>14,15,18</sup>

## DIAGNOSIS

The main problem in abdominal TB is diagnostic and management issues. The symptoms and signs of abdominal TB are usually not specific and resembles to other diseases.<sup>1,2,3</sup>

Abdominal TB is established based on history of the disease, physical examination, lab examination and other diagnostic examination as well as good response

after TB treatment. Abdominal TB can occur with or without pulmonary TB.<sup>1,2,3,12,13</sup>

Presumptive diagnosis can be made if an active pulmonary TB is found and/or accompanied with clinical or radiologic findings that are consistent to intestinal TB. It is essential to remember that positive chest X-ray findings were found in less than 50% of patients.<sup>2,3,13,19,20</sup>

The definite diagnosis is based on histological findings, Ziehl-Neelsen staining of the acid-fast bacilli, and culture, although the sensitivity of each examination was reported to be various. Colonoscopy with biopsy is one of the non-operative diagnostic approach which is useful for acknowledging ileocaecal TB.<sup>19,20,21</sup> The combination of histological examination and culturing biopsy material can establish the diagnosis in more than 80% of patients.<sup>11,21,22,23</sup>

Deep biopsy per endoscopy is best performed on the margin and the base of the ulcer, considering granuloma of TB are often located in submucosal area. This situation is different with the granuloma found in Crohn's disease, which are usually located in the mucosa.<sup>19,20,22,23</sup>

PCR examination from biopsy specimens can help in establishing the diagnosis with higher sensitivity and specificity in comparison to urine culture and the result can be obtained in a relatively short period of time.<sup>19,20,23,24,25</sup> Anti-cord factor antibodies with ELISA is also regarded as being useful in establishing intestinal TB fast and in helping to differ it from Crohn's disease.<sup>23,24</sup>

In gastrointestinal TB, endoscopy finding is not pathognomonic. Finding granuloma and positive acid-fast bacilli from the biopsy of tissue obtained through endoscopy are also rare occasions. TB can happen in all segments of the gastrointestinal tract. The region most commonly affected is the ileocaecal region and the caecum.<sup>18,22,23,26</sup>

Through colonoscopy, features can be found including hyperemic mucosa with erosion and edema, some with bleeding, visible multiple polypoid mass in ileocaecal valve and terminal ileus (giving the differentials of TB, Crohn's, and malignancy) with multiple ulcerations in the rectum, ascending colon, and caecum. Segmental or isolated colonic TB comprises of 9.2% of all abdominal TB cases, and it usually affects sigmoid colon, ascending colon, and transversal colon. Multifocal involvement was seen in 28-44% of patients with colitis TB.<sup>22,23,26</sup>

Lee et al in a prospective analysis of endoscopic findings, created a scoring system in measuring the probability of Crohn's disease as well as intestinal TB with positive prediction values of 94.9% and 88.9%, respectively.<sup>27</sup> Endoscopic findings supporting Crohn's disease include anorectal lesion, longitudinal

ulcer, aphthous ulcer, and cobblestone appearance, whereas endoscopic findings supporting intestinal tuberculosis include transversal ulcer, polypoid mass, the involvement of less than four segments, and ileocaecal-valve lesion.<sup>18,26</sup>

Histological features of the result of colon biopsy often show active chronic colitis with cryptic destruction giving the differentials of inflammatory bowel diseases (IBD) and chronic bacterial/parasitic infection. Pulimoid et al in a study on the result of colonoscopic biopsy, concluded that the histologic features of mucosal biopsy might aid in separating cases of intestinal TB and Crohn's disease, but multiple biopsy from different segments are required.<sup>28</sup> It was also said that the accuracy of diagnosis is directly proportional to the amount of biopsy performed from rectum to the ileus.<sup>21,22,24</sup>

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of ileocaecal TB includes actinomycosis, amebiasis, *Yersinia enterocolitis*, Crohn's disease, lymphoma, and adenocarcinoma. Biopsy helps in identifying lymphoma or carcinoma cell. Amebiasis is usually acute in nature even though some patients may experience chronic colitis or colon ameboma. Biopsy obtained from the ulcers found in mostly normal mucosa may contain the trophozoic phase of *Entamoeba histolytica*. The microorganism is usually found in patient's stools and amoeba serology shall give positive result.<sup>21,24,29</sup>

**Table 5. Differential diagnosis of abdominal tuberculosis<sup>17</sup>**

Symptom	Differential diagnosis
Malabsorption	Coeliac disease
	Lymphoma
	Immunoproliferative small intestinal disease
Mass	Caecal carcinoma
	Appendicular mass
	Crohn's disease
Ascites	Cardiac disease
	Renal disease
	Hepatic disease
	Malignancy

## MANAGEMENT

Therapy with standard anti-tuberculosis drugs has a high efficacy on intestinal TB. Compliance is the main point which determines the success of therapy.<sup>27,30</sup>

Khan et al reported a small group of patients whose diagnosis of abdominal TB was hard to establish and the therapy trial using anti-tuberculosis drugs can be taken into consideration within tight monitoring.<sup>24</sup>

A study on abdominal TB in India also mentioned

that if a strong clinical suspicion is found in an endemic area, empirical therapy using anti-tuberculosis is allowed. Another study conducted by Ramanathan et al concluded that justifying the initiation of anti-tuberculosis drugs therapy in an endemic area based on clinical suspicion and adequate response should be acceptable as a diagnostic basis of abdominal TB although histopathological or microbiology confirmation was not possible.<sup>12</sup>

Marshall JB, in a study on the length of TB treatment, mentioned that a therapy regimen of 6, 9, or 18 to 24 months all were proven effective in the management of extrapulmonary TB. Systemic symptoms such as fever, anorexia, and weight loss can decline in 4 to 6 weeks, whereas gastrointestinal symptoms require a longer time.<sup>7</sup>

In a study conducted in Saudi Arabia, it was reported that corticosteroid reduce the frequency of recurrent abdominal pain, intestinal obstruction, and surgical procedure as well as mortality rate. It was then suggested also to give corticosteroid especially in the case of peritonitis TB.<sup>8,9,28</sup>

## CONCLUSION

Clinical manifestations of abdominal TB are not specific. In a way, detailed diagnostic approaches and supporting results are needed to determine the final diagnosis. On the other side, there is no single examination, be it clinical symptoms, laboratory, radiology, endoscopy, microbiology or histopathological examinations are adequate to diagnose abdominal TB. Diagnostic approach to abdominal TB remains a challenge for clinicians; aside from the need of strong clinical judgment. If the diagnosis can be quickly established, this disease would then be able to be treated with conventional anti-tuberculosis drugs. Therapy for 6, 9 and 18 to 24 months are all proven to be effective in the management of extrapulmonary TB.

In countries with high prevalence of abdominal TB, initiating a trial of anti-tuberculosis treatment is allowed if it is accompanied by consistent clinical features. Diagnosis can be established when the patient responds to anti-TB treatment.

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