**World Gastroenterology Organisation Global Guidelines**

# Digestive tract tuberculosis

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# 1 Introduction

> "Diarrhea attacking a person affected with phthisis is a mortal symptom."
> — Hippocrates, *Aphorisms* 5.14

> "It is impossible to diagnose abdominal tuberculosis with any degree of certainty, since the disease mimics many other abdominal conditions and histological confirmation may be equivocal."
> — Joseph Walsh, *Transactions of the National Association for the Study and Prevention of Tuberculosis* 1909;5:217–22

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis,* typically causing pulmonary TB. TB is the ninth most frequent cause of death worldwide and is the leading cause due to a single infectious agent, ranking above human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS).

In 2017, 10 million people developed TB disease and 1.6 million died of it, including 0.3 million among people with HIV—TB is the leading killer of HIV-positive people [1].

- About one-quarter of the world's population have latent TB.0
- People infected with TB bacteria have a 5–15% lifetime risk of falling ill with TB. However, persons with compromised immune systems, such as people living with HIV, malnutrition, diabetes, those taking immunosuppressive drugs, and people who use tobacco, have a much higher risk of falling ill.
- Multidrug-resistant TB (MDR-TB) continues to be a public health issue and a health security threat. The World Health Organization (WHO) estimates that there were 558,000 new patients with resistance to rifampicin—the most effective first-line drug—among whom 82% had MDR-TB.
- Globally, the incidence of TB is falling at about 2% per year.
- An estimated 60 million lives were saved through TB diagnosis and treatment between 2000 and 2019 [1].

Abdominal tuberculosis is uncommon in comparison with pulmonary TB. Gastrointestinal TB makes up 2.5% of extrapulmonary cases in the United States [2].

- Lymph-node disease is the most common presentation of extrapulmonary TB (EPTB), both in individuals with HIV infection and HIV-seronegative patients.
- Pleural TB accounts for approximately 20% of all EPTB cases.
- Genitourinary TB accounts for 10–15% of all cases of EPTB in the U.S.

Early diagnosis remains difficult, due to the nonspecific clinical presentation of TB, which can mimic other gastrointestinal diseases and may vary from an acute to a chronic abdomen in areas endemic for TB. While some may benefit from antitubercular therapy, others may develop surgical problems such as strictures, obstruction, fistulas, or perforations, which may necessitate surgical intervention.

HIV infection is a major risk factor for the development of TB, and peritoneal tuberculosis is a real medical challenge in immunocompromised patients due to its insidious and nonspecific symptoms.

Although any area of the gut can be involved, tuberculous involvement of the gastrointestinal tract is most frequently seen in the ileocecal area, the ileum, and the colon. The ileocecal area is most commonly affected by TB. Explanations for this include its high density of lymphoid tissue, slowing of intestinal transit, and low concentration of bile acids [3].

Tuberculous peritonitis needs to be considered in all cases of unexplained exudative ascites. Other locations for abdominal TB infection are: spleen, liver, and lymph nodes [3–6].

## 1.1 About WGO cascades

**WGO cascades: a hierarchical set of diagnostic, therapeutic, and management options for dealing with risk and disease, ranked by the resources available.**

World Gastroenterology Organisation (WGO) guidelines and cascades are intended to highlight appropriate, context-sensitive and resource-sensitive management options for all geographical areas, regardless of whether they are "developing," "semi-developed," or "developed." WGO cascades are context-sensitive, and the context is not necessarily defined solely by resource availability.

The cascade options presented here for both the diagnosis and management of gastrointestinal tuberculosis are key and represent the most important part of this document. Particular emphasis is placed on gold-standard, medium-resource, and low-resource categories.

For the "Cascades for diagnosing gastrointestinal TB," see Section 3.1 below.

## 1.2 Definitions

- Abdominal TB: TB of the gastrointestinal tract and any other organ within the abdominal cavity, excluding esophageal tuberculosis.
- Intestinal TB: nonperitoneal gastrointestinal tract TB.
- Peritoneal TB: tuberculosis of the peritoneum.

## 1.3 Epidemiology

Table **1** Estimated epidemiological burden of tuberculosis in 2017

| Region | Population (× 1 million) | TB mortality, best estimate (× 1000) | | TB incidence, best estimate (× 1000) | | MDR/RR-TB incidence (× 1000) |
|---|---|---|---|---|---|---|
| | | HIV-negative | HIV-positive | Overall | HIV-positive | |
| High TB * | 4760 | 1110 | 247 | 8720 | 766 | |
| Africa | 1047 | 413 | 252 | 2480 | 663 | 90 |
| Americas | 1006 | 18 | 6 | 282 | 30 | 11 |
| Eastern Mediterranean | 682 | 89 | 3 | 771 | 9.8 | 41 |
| Europe | 920 | 24 | 5 | 273 | 33 | 109 |
| South-East Asia | 1968 | 638 | 28 | 4440 | 152 | 192 |
| Western Pacific | 1901 | 92 | 5 | 1800 | 31 | 114 |
| *Global* | 7523 | 1270 | 300 | 10000 | 920 | 558 |

HIV, human immunodeficiency virus; MDR, multidrug-resistant; RR, rifampicin-resistant; TB, tuberculosis.

* "High TB": 30 countries with a high TB burden, according to the World Health Organization (Angola, Bangladesh, Brazil, China, DPR Korea, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Thailand, UR Tanzania, Vietnam, Cambodia, Central African Republic, Congo, Lesotho, Liberia, Namibia, Papua New Guinea, Sierra Leone, Zambia, Zimbabwe). For data for all countries, see www.who.int/tb/data or https://www.who.int/tb/publications/global_report/gtbr2018_annex4.pdf?ua=1

*Source:* World Health Organization, Global tuberculosis report 2018 [7].

### 1.3.1 WHO 2018 global tuberculosis report [1,7]

- TB occurs in every part of the world. In 2017, the largest number of new TB cases occurred in the South-East Asia and Western Pacific regions, with 62% of new cases, followed by the African region, with 25% of new cases.
- There were cases in all countries and age groups, but overall 90% of the patients were adults (aged ≥ 15 years) and 9% were people living with HIV (72% of them in Africa).
- In 2017, 87% of new TB cases occurred in the 30 countries with a high TB burden, and two-thirds were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%), and South Africa (3%).
- Only 6% of global cases were in the WHO European Region (3%) and WHO Region of the Americas (3%).
- The severity of national epidemics varies widely among countries. In 2017, there were fewer than 10 new cases per 100,000 population in most high-income countries, 150–400 in most of the 30 countries with a high TB burden, and above 500 in a few countries, including Mozambique, the Philippines, and South Africa.

- Drug-resistant TB continues to be a public health crisis. Three countries accounted for almost half of the world's cases of multidrug-resistant/rifampicin-resistant (MDR/RR) TB: India (24%), China (13%), and the Russian Federation (10%).
- Globally, 3.5% of new TB patients and 18% of previously treated patients had MDR/RR-TB. The highest proportions (> 50% in previously treated patients) are in countries of the former Soviet Union. Among patients with MDR-TB in 2017, 8.5% (95% confidence interval, 6.2% to 11%) were estimated to have extensively drug-resistant TB (XDR-TB).
- The geography of the disease is changing, in Western countries mainly due to immigration, HIV, and the development of multidrug-resistant strains of TB [8].
- In some Western countries, abdominal TB is mostly "imported" rather than "home-grown" TB.
- The European Crohn's and Colitis Organization (ECCO) guidelines point out that just spending time in a country with a high incidence of TB also raises individuals' risk [9].

The incidence of intestinal TB (ITB) has increased in parallel with the overall increase in the prevalence of tuberculosis. One in five TB patients in the European Union has extrapulmonary tuberculosis [10]. The incidence of Crohn's disease (CD) has also increased over the past several decades all over the world, including those areas where the disease has conventionally been reported to be rare [11].

## 1.4 Etiopathogenesis and risk factors

Tuberculosis flourishes wherever there is poverty and overcrowding; 5–15% of the estimated 1.7 billion people infected with *M. tuberculosis* (MTB) will develop overt clinical TB disease during their lifetime [12].

The probability of developing TB disease is much higher among people infected with HIV, and it is also higher among people affected by risk factors [13] such as:

- Other causes of immunosuppression—corticosteroid therapy, immunosuppressive or chemotherapeutic treatment, following treatment with anti-tumor necrosis factor (TNF) agents or other biological treatment, and patients undergoing continuous ambulatory peritoneal dialysis.
- Chronic debilitating diseases—diabetes mellitus, hematological diseases, and chronic lung disease, particularly silicosis.
- Malnutrition, underlying malignancy, cirrhosis, alcoholism.
- Elderly patients.
- Incarcerated and institutionalized individuals at risk of TB.
- Traveling to countries with a high incidence of TB.

Extrapulmonary disease is more common in patients with HIV:

- In 2016, globally, 57% of notified TB patients had a documented HIV-positive test result, up from 55% in 2015. In the WHO African Region, where the burden of HIV-associated TB is highest, 82% of TB patients had a documented HIV-positive test result (up from 81% in 2015) [12].
- The diagnosis of tuberculosis may precede the diagnosis of AIDS by several months; tuberculosis frequently disseminates in AIDS patients, progresses rapidly, and is associated with a high mortality rate [14].

Abdominal tuberculosis may occur due to:

- Reactivation of a dormant primary gastrointestinal focus:
  — Originating through hematogenous spread from a pulmonary focus acquired during primary infection in childhood.
  — Or caused by swallowed bacilli transported by macrophages through the lymphatics to the mesenteric lymph nodes, where they remain dormant.
- Ingestion of bacilli from an active pulmonary focus.
- Hematogenous spread from active tuberculosis in other organs.
- Direct extension from adjacent organs.
- Ingestion of infected milk:
  — The practice of drinking unpasteurized milk, especially by children when they are working as shepherds in some parts of the world, such as in the highlands region of Pakistan and other regions of central Asia, is a cause of abdominal TB.
  — This is rarely a cause in Western countries, due to the disappearance of bovine tuberculosis, pasteurization of milk, and the practice of boiling milk before consumption in developing countries.

Reactivation of a latent TB focus may be caused by immune suppression due to advanced age, HIV/AIDS infection, anti-TNF therapy, malnutrition, weight loss, alcoholism, diabetes, chronic renal failure, and other conditions [12,14,15].

# 2 Clinical features

## 2.1 Locations

*Pulmonary TB.* Most cases of TB are pulmonary (Fig. **1**). Among patients with extrapulmonary TB, only 15–20% have concomitant active pulmonary tuberculosis [8]. Pulmonary TB is not covered by this guideline.

*Extrapulmonary TB.* Extrapulmonary TB can be found in the following locations: larynx, lymph nodes, pleura, brain, kidneys, bones and joints, peritoneum and intestines, meninges, skin, and pericardium. Clinicians will continue to see cases, due to the resurgence of tuberculosis that has been taking place since the mid-1980s in many countries. Extrapulmonary TB is found more often in HIV-infected or other immunosuppressed individuals, and young children. With the exception of abdominal TB, extrapulmonary TB is not covered by this guideline.

*Miliary TB.* A third, but rare, form of TB is miliary TB, in which tubercle particles are carried to all parts of the body through the bloodstream. Miliary TB is not covered by this guideline.

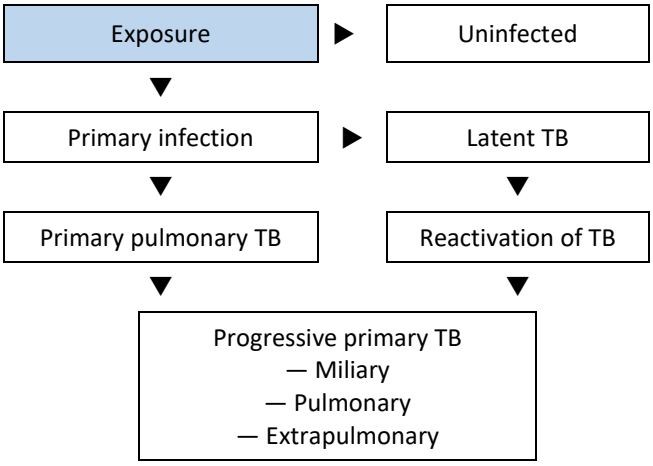


Fig. **1** Natural development of tuberculosis infection

*Abdominal TB.* Tuberculosis can involve any part of the gastrointestinal tract, from the mouth to anus (49%), peritoneum (42%), mesenteric lymph nodes (4%), and the solid viscera, including the liver and pancreaticobiliary system (5%) [13,16]. The most common site of involvement in intestinal TB is the ileocecal region, followed by the colon and jejunum.

- Abdominal TB is predominantly a disease of young adults.
- In a large case series, digestive tract tuberculosis was located in the upper gastrointestinal tract in 8.5% of cases, in the small bowel in 33.8%, in the large bowel in 22.3%, in the peritoneum in 30.7%, and in the liver in 14.6% [17].

## 2.2 Symptoms and physical signs

The symptoms and signs of gastrointestinal and peritoneal tuberculosis are nonspecific, and the diagnosis may be missed or delayed—resulting in increased morbidity and mortality.

Most patients with abdominal tuberculosis present with symptoms that have lasted from 1 month to 1 year. These patients may present with abdominal pain, wasting, weight loss in general, loss of appetite, fever, diarrhea, constipation, rectal bleeding, and edema [18]. The symptoms are usually of moderate intensity.

The presence of coexistent pulmonary TB significantly increases the frequency of fever and night sweats, weight loss, and pulmonary symptoms.

TB may be associated with a number of immune-mediated manifestations such as erythema nodosum, erythema induratum, reactive arthritis (Poncet disease) and uveitis, all of which may mimic extraintestinal manifestations of Crohn's disease [19–22].

Table **2** Clinical symptoms and features of digestive tract tuberculosis [14,15,17]

| Site | Type | Symptoms and features |
|---|---|---|
| Small intestine | Ulcerative | Diarrhea, malabsorption<br>Systemic symptoms of TB infection |
| | Strictural | Obstruction |
| Large intestine | Ulcerative | Rectal bleeding |
| | Hypertrophic | Lump, obstruction |
| Peritoneal | Ascitic | Ascites, abdominal pain, distension, fever, systemic symptoms of TB infection |
| | Adhesive | Obstruction |
| Lymph nodes | | Lump, abdominal pain, fever, systemic symptoms |
| Liver | | Fever, malaise, weight loss, jaundice, abdominal pain and hepatomegaly |
| Pancreas | | Epigastric pain, fever and weight loss, jaundice, gastrointestinal bleeding |

The *physical examination* may reveal pallor, ascites or doughy abdomen, and generalized abdominal tenderness, especially in the right iliac fossa. Patients may have hepatomegaly and abdominal masses due to liver involvement, enlarged lymph nodes, adherent bowel loops, or a cold abscess [13].

The *symptoms and signs* of abdominal TB are nonspecific and may very much resemble CD and other gastrointestinal pathology. TB may be confused with cancers of the relevant areas. Intestinal TB has been identified in asymptomatic patients who undergo colonoscopies for other reasons.

Pain is the most common presentation in about 85%, weight loss in 66%, fever in 35–50%, and diarrhea in 20% of patients.

- *Systemic manifestations* can be found in 30% of patients, such as low-grade fever, rise of temperature in the evening, lethargy, malaise, night sweats, and weight loss. This is more commonly seen with the ascitic type of tubercular peritonitis and ulcerative lesions of the intestine.
- *Abdominal tenderness* is found in most patients, and an abdominal mass, usually in the right lower quadrant, in 25–50% of patients.
- *Malabsorption* can be seen in 21–75% of cases [4].
- *Acute abdomen:* in developing countries, extrapulmonary (abdominal) TB may often present as an acute abdomen in surgical emergencies such as perforations and obstructions of the gut [4].
- *Ascites* can be caused by peritoneal tuberculosis or can originate from hepatic, malignant, cardiac, renal, and other infectious diseases [23].

- *Peritoneal TB* with ascites may present with less tenderness and guarding than pyogenic peritonitis with perforation.
- *Abdominal cocoon* is an uncommon form of abdominal tuberculosis, characterized by the formation of a fibrous membrane-like sac around the small-intestinal loops. Conservative management with antitubercular therapy (ATT) may suffice in some patients, whereas nonresponsive patients require surgery [24].
- *Anorectal TB* may present as stricture, fistula in ano, or anal fissure.
- *Gastric TB* may mimic peptic ulcer or carcinoma, or may present with perforation or gastric outlet obstruction. It appears more commonly with fistulas in the antral mucosa than in the body of the stomach, and quite commonly presents with pyloric stenosis.
- *Duodenal TB:* patients often present with symptoms of obstruction due to luminal strictures [25], and they may present with a history of dyspepsia. However, submucosal infiltration without clear lymph-node necrosis (LNN) occurs.
- *Esophageal TB:* rare; constitutional symptoms, dysphagia, odynophagia, retrosternal discomfort, pain [18]; may be confused with cancers of the relevant areas.
- *Ileocecal and small-bowel TB* may present with a complication such as intestinal obstruction, sometimes fistulas to the colon or bladder, perforation, or malabsorption, especially in the presence of a stricture.
- *Rectal TB:* hematochezia is the most common symptom, followed by constitutional symptoms and constipation; an anular stricture may be found on digital examination, with focal areas of deep ulceration.
- *Hepatic TB* is usually insidious and often nonspecific. The patient may present with protracted illness, frequently associated with fever, malaise, weight loss, jaundice, abdominal pain, and hepatomegaly. Liver involvement may be in the form of granulomatous disease, or a part of miliary TB, or localized hepatic disease presenting as local abscess. Biliary tract involvement may be due to enlarged tuberculous lymph nodes or due to inflammatory strictures, and may cause obstructive jaundice.
  — The liver is usually not tender on percussion or palpation.
  — Splenomegaly may be present in some cases.
  — These patients are usually anemic.
  — Mild jaundice may be present, and may become severe.
- *Pancreatic TB* is more common in women.
  — It presents with epigastric pain, fever, and weight loss; jaundice may or may not be present.
  — Other clinical presentations include acute or chronic pancreatitis and gastrointestinal bleeding secondary to splenic or portal vein thrombosis.
  — It should be suspected in young patients who have a pancreatic mass or hypodense lymph nodes in the peripancreatic region, particularly if they present with fever, without jaundice, are living in a TB-endemic area, or have been exposed to TB in the past.

**TB should always be considered in the differential diagnosis of unusual gastrointestinal presentations, especially in high TB-endemic areas.**

*Sources:* [4,17,18,23] and other references mentioned in the text above.

# 3 Diagnosis

## 3.1 Cascades for diagnosing gastrointestinal TB

Cascades of context-sensitive and resource-sensitive options/alternatives for countries and regions with different levels of resources and access, and with different cultures and epidemiology.

Table **3** Cascade: diagnosis of abdominal tuberculosis

| Resource level | Diagnostic options |
|---|---|
| High categories | • Clinical risk assessment<br>• Chest x-ray<br>• Acid-fast smear microscopy in sputum<br>• Abdominal ultrasound<br>• EUS with FNA or FNB<br>• Upper GI endoscopy (if suspicion of upper GI tract tuberculosis)<br>• Abdominal x-rays, erect and supine (obstruction)<br>• CT of the abdomen (with intravenous and negative oral contrast)<br>• IGRA<br>• Ileocolonoscopy and enteroscopy<br>• Endoscopic biopsy for histopathology, culture, TB PCR and GeneXpert MTB RIF<br>• Ascitic fluid for TLC, DLC, total protein, albumin, culture, PCR and GeneXpert and adenosine deaminase levels<br>• Laparoscopy and biopsy |
| Medium categories | • Clinical risk assessment<br>• Chest x-ray<br>• Acid-fast smear microscopy in sputum<br>• Abdominal ultrasound<br>• Abdominal x-rays, erect and supine (obstruction)<br>• CT of the abdomen (with intravenous and negative oral contrast)<br>• Colonoscopy<br>• Endoscopic biopsy for histopathology<br>• Ascitic fluid for TLC, DLC, total protein, albumin, culture<br>• Adenosine deaminase levels<br>• Laparoscopy and biopsy |
| Low categories | • Clinical risk assessment<br>• Purified protein derivative (PPD) skin test<br>• Chest x-ray<br>• Acid-fast smear microscopy in sputum<br>• Abdominal ultrasound<br>• Barium contrast studies<br>• Abdominal x-rays, erect and supine (obstruction)<br>• Ascitic fluid for TLC, DLC, total protein, albumin |

CT, computed tomography; DLC, differential leukocyte count; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; FNB, fine-needle biopsy; GI, gastrointestinal; IGRA, interferon-gamma release assay; MTB, *Mycobacterium tuberculosis*; PCR, polymerase chain reaction; PPD, purified protein derivative; RIF, resistance to rifampicin; TLC, total leukocyte count.

Currently, there is no gold standard for the diagnosis of latent TB infection and early detection of active TB; accordingly, no single test is adequate for the diagnosis of abdominal

tuberculosis in all patients. Abdominal TB in non-HIV patients remains an ongoing diagnostic dilemma, requiring a high index of clinical suspicion [16].

**Abdominal TB should always be considered as one of the differential diagnoses of an acute or chronic abdomen in endemic areas [4] and in specific situations in developed countries, such as in HIV patients and patients receiving treatment with immunosuppressive drugs or biologics.**

A definitive diagnosis of gastrointestinal TB can be made if any of the following four criteria are present [26]:

- Culture of tissue (colonic biopsy, lymph nodes) positive for *M. tuberculosis*
- Histological demonstration of typical acid-fast bacilli (AFB)
- Histological evidence of caseating granuloma
- GeneXpert MTB rifampicin (RIF) assay/TB polymerase chain reaction (PCR) done on a biopsy specimen.

A diagnosis of *peritoneal TB* should be considered in the differential diagnosis of exudative ascites (protein > 2.5 g/dL) with a lymphocyte predominance and/or a serum-ascitic albumin gradient of < 1.1 mg/dL. Adenosine deaminase levels are elevated. Microbiological or pathological confirmation remains the gold standard for diagnosis [27].

A diagnosis of *intestinal TB* [28] should be based on:

- At least eight biopsies performed during the colonoscopy for histopathologic evaluation.
- Acid-fast bacillus (AFB) tissue testing and culture—positivity on any result is diagnostic; however, a negative result does not exclude a diagnosis of intestinal TB.
- Tissue PCR evaluation is recommended; a positive result is significant.
  — Testing can be carried out in old specimens retrospectively.
  — A negative result does not exclude the diagnosis of TB.
- A positive purified protein derivative (PPD) test and a positive interferon-gamma release assay (IGRA) test.
  — Positive PPD is a common finding in developing countries, including in Crohn's disease and other causes of ascites.
  — PPD or IGRA testing is used in high-resource countries to diagnose previous exposure to tuberculosis.
  — PPD or IGRA testing cannot be used to establish a diagnosis of abdominal TB, especially in developing countries where high exposure to TB and bacille Calmette–Guérin (BCG) vaccination are encountered.

## 3.2 Investigation

Despite advances in diagnostic methods, a considerable proportion of the TB cases reported to the World Health Organization are still diagnosed clinically rather than being confirmed bacteriologically, due to a lack of funding or a lack of local expertise. In 2016, less than 60% of the pulmonary cases reported to the WHO were bacteriologically confirmed [12].

Table **4** Clinical and laboratory features of peritoneal tuberculosis [27,29]

| **Clinical features** | | **Frequency (%)** |
|---|---|---|
| Systemic symptoms | Fever | 59 |
| | Weight loss | 61 |
| Abdominal symptoms | Abdominal pain | 64.5 |
| | Diarrhea | Up to 21 |
| | Abdominal tenderness | 47.7 |
| Signs | Ascites | 73 |
| | Abdominal mass | 6–40 |
| **Laboratory findings** | | **Sensitivity (%)** |
| Positive PPD skin test | | 38 |
| Abnormal chest radiograph | | 19–83 |
| Ascitic fluid | Protein > 3 g% | 84–100 |
| | Lymphocyte predominance | 68 |
| | ADA | Up to 100 |
| | AFB smear | 3 |
| | Culture | 35 |
| | Interferon gamma assay | 93 |
| PCR in ascitic fluid | | 93 |

ADA, adenosine deaminase; AFB, acid-fast bacilli; PPD, purified protein derivative.

### 3.2.1 Routine lab tests

*Routine laboratory tests* reveal mild anemia and an increased sedimentation rate in 50–80% of patients. The white blood count is usually normal [18].

### 3.2.2 Radiology

*Computed tomography (CT) scanning* with oral contrast is the most helpful imaging modality for assessing intraluminal and extraluminal pathology. It can show the location and extent of the inflammatory process and involvement of the intestine, mesentery, peritoneum, lymph nodes, and solid organs, as well as retroperitoneal disease [17,18,30]. It can discriminate between carcinomatous ascites and peritoneal tuberculosis. The presence of necrotic lymph nodes is diagnostic for peritoneal tuberculosis. If applicable, CT enterography can detect and map the involved small bowel.

*Ultrasound.* Endoscopic ultrasonography (EUS) can help with the imaging of various lesions close to the gastrointestinal lumen, and they can also be aspirated or biopsied using EUS-guided fine-needle aspiration or biopsy [31]. Targeted biopsies from the lymph nodes, liver, and pancreas may be taken [32]. EUS is useful for imaging peritoneal tuberculosis [18].

*Magnetic resonance imaging* (MRI) cannot detect small calcifications within nodes or masses and is not helpful for distinguishing between Crohn's disease and intestinal TB.

*Chest x-ray*. A negative chest x-ray does not exclude abdominal TB.

### 3.2.3 Endoscopy

*Endoscopy* with biopsy may be useful for diagnosing intestinal TB if the area of the affected gut is within reach of a flexible endoscope. Not infrequently, the disease is not considered until it is diagnosed at the time of surgery [8]. Double-balloon enteroscopy may be helpful for obtaining biopsies. In case of duodenal infiltrate without clear ulcers, performing polypectomy after banding may be helpful for obtaining better biopsies [25].

- Rapid diagnosis of intestinal TB is possible if acid-fast bacilli or caseating granulomas are seen on the biopsied tissue.
- For peritoneal tuberculosis, endoscopy should be done to exclude primary digestive cancer (carcinomatous ascites).
- Enteroscopy and capsule endoscopy can be used to investigate small-intestinal disease. Capsule endoscopy must be avoided in patients with a suspected stricture.

### 3.2.4 Laparoscopy

*Laparoscopy* with a biopsy is used to diagnose peritoneal TB, but its role is less clear in intestinal TB [17]. Laparoscopy with a directed biopsy allows rapid, specific diagnosis [8].

- Diagnostic laparoscopy findings may include: thickened peritoneum, ascites, whitish nodules, lymph nodes, fibrotic adhesions, and hepatomegaly.
- Intestinal fat wrapping is unusual in intestinal TB [33,34] and would favor a diagnosis of Crohn's disease.

### 3.2.5 Pathology

*Biopsies* show acid-fast bacilli or caseating granulomas in case of TB, but acid-fast bacilli staining lacks sensitivity and specificity. Distinguishing between Crohn's disease (CD) and TB is never completely straightforward, and although it is rare, the two can coexist, especially during biological therapies.

Making a diagnosis of intestinal TB with endoscopy and mucosal biopsy is difficult, as the disease is submucosal and the diagnostic yield is poor (demonstrating AFB, positive TB PCR, caseating granulomas, or a positive TB culture). Pulimood and others have described a number of histological features on mucosal biopsy specimens which, in the absence of acid-fast bacilli and caseating granulomatous inflammation, are diagnostic of intestinal TB [35–37]. These include confluent granulomas, multiple granulomas in a given biopsy site, large granuloma size, bands of epithelioid histiocytes lining ulcers, submucosal granulomas, and disproportionate submucosal inflammation—i.e., submucosal inflammation that significantly exceeds mucosal inflammation.

Histopathological findings may include nonspecific inflammatory changes:

- Tissue for histopathology may be obtained during surgery, colonoscopy, CT, or ultrasound-guided biopsy, laparoscopy, and upper gastrointestinal endoscopy.

- Tuberculosis is a chronic granulomatous inflammatory disease, but granulomas may be missing in a given sample.
- Intestinal lesions may be ulcerative (60%), hypertrophic (10%), and ulcerohypertrophic (30%) [13].
- If the suspicion of tuberculosis is high, the material should be sent for microbiological analysis [31] and molecular testing.

*Acid-fast smear microscopy* involves bacterial examination of biological fluids in patients with suspected abdominal TB.

- A high rate of negativity in sputum, urine, and ascites specimens is reported by the majority of studies. The probability of a positive acid-fast smear may increase with the number of sites sampled [4].
- The technique was developed more than 100 years ago, with sputum samples being examined using a microscope to determine the presence of bacteria. In the case definitions currently recommended by the WHO, one positive result is required for a diagnosis of smear-positive pulmonary TB.
- Stool staining for AFB is not recommended, as commensal non-TB mycobacteria can lead to a false-positive diagnosis of intestinal TB.

### 3.2.6 Microbiology

*Culture-based methods.* These are the current reference standard. They require a more developed laboratory capacity; biopsy culture for MTB is time-consuming (from 3–8 weeks up to 12 weeks to provide results) [12], and the results are frequently negative (with an accuracy ranging from 25% to 35% [17] and even lower in other studies).

### 3.2.7 Serological testing results

*Rapid molecular tests.* The only rapid test for diagnosing TB currently recommended by the WHO is the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, California, USA).

- It can provide results within 2 hours, and was initially recommended (in 2010) for the diagnosis of *pulmonary TB in adults.* Since 2013, it has also been recommended for use in *children* and to diagnose *specific forms of extrapulmonary TB.* The test has much better accuracy than sputum smear microscopy [12].
- For diagnosing *abdominal TB,* an Indian review article reports a study from Delhi in patients with intestinal TB, with a low sensitivity for diagnosing intestinal TB: only three of the 37 patients (8%) had a positive Xpert result. In peritoneal TB, two reports suggest that the sensitivity of Xpert is also low, with 12 of 67 suspected cases (17.9%) in one series and four of 21 (19%) cases in another series being positive for Xpert [38].
- A 2015 meta-analysis of 36 studies concluded that Xpert has a high level of specificity but limited sensitivity for detecting *extrapulmonary TB* (EPTB). Positive Xpert test results may be useful for fast identification of EPTB cases, but negative test results provide less certainty in ruling out disease [39].
- A 2018 study analyzing GeneXpert MTB/RIF for the diagnosis of abdominal tuberculosis (data from 21 patients) found that the sensitivity of GeneXpert was 28.57% and its specificity was 0%. The authors concluded that in their study, GeneXpert showed poor sensitivity and specificity for detecting abdominal TB from ascitic fluid samples.

*Interferon-gamma release assay* (IGRA). IGRA is based on the stimulation of a cellular immune response by the immunodominant antigens ESAT-6 and CFP10 specific to MTB, and it provides a diagnostic alternative to the tuberculin skin test.

IGRA test options include:

- QuantiFERON-TB Gold In-Tube test (QFT, Qiagen, Hilden, Germany), based on whole blood. The accuracy of this test is reduced in patients who are receiving immunosuppressive agents [40].
- T-SPOT.TB test (enzyme-linked immunospot/ELISPOT, Oxford Immunotec, Abingdon, UK), based on purified peripheral blood mononuclear cells.

Various studies have confirmed the informational value of these tests in diagnosing TB, and the emergence of IGRA tests may improve the identification of latent tuberculosis infection (LTBI) [41].

The main advantages of these tests are:

- They are not affected by a previous BCG vaccination.
- There is no cross-reaction with most nontuberculosis mycobacteria.
- The can be completed at a single visit.

Disadvantages are:

- The cost of the tests, at US$ 100 or more, may prevent them from being recommended in low-income countries.
- They require a specially equipped laboratory, trained personnel, and invasive procedures.
- IGRA does not distinguish between active and latent TB infections.
- A negative IGRA does not rule out LTBI.
- The tests cannot predict the progression of latent tuberculosis [11].

Although it is still difficult to determine superiority between the IGRAs and the tuberculin skin test (TST), both are negatively affected by immunosuppressive therapy. Screening before starting immunosuppressive therapy should therefore be considered. It is imperative for all patients to receive screening prior to anti-TNF therapy [40].

IGRA may be used as part of the overall risk assessment to identify individuals for preventive treatment (e.g., immunocompromised persons, children, close contacts, and recently-exposed individuals) [42], but due to the above-mentioned disadvantages, IGRA tests are not suitable for large-scale screening studies, particularly among children.

Determination of interferon-gamma levels in ascitic fluid may be a technique with future application in the diagnosis of peritoneal TB [27].

The European Centre for Disease Prevention and Control (ECDC) has published the following guidance on the use of interferon-gamma release assays to support the diagnosis of TB [42]:

- IGRAs should not replace the standard diagnostic methods (including microbiology, molecular tests, and clinical and radiological assessment) for diagnosing active TB.
- IGRAs do not have any added value in most clinical situations when combined with standard methods for diagnosing active TB.
- However, based on limited evidence, in certain clinical situations (e.g., patients with extrapulmonary TB, patients who test negative for acid-fast bacilli in sputum and/or

negative for *M. tuberculosis* on culture, TB diagnosis in children, or in the differential diagnosis of infection with nontuberculous mycobacteria), IGRAs may contribute supplementary information as part of the diagnostic work-up. A negative IGRA does not rule out active TB.

- On the basis of the available results for the positive predictive value (PPV) for assessing progression and taking into consideration the low statistical power and small number of studies, IGRAs may be used as part of the overall risk assessment to identify individuals for preventive treatment (e.g., immunocompromised persons, children, close contacts, and recently-exposed individuals).
- Similarly, despite the limitations of available studies, the high negative predictive value (NPV) of IGRAs for assessing progression indicates that at the time of testing and in the context of an overall risk assessment, progression to active TB in healthy immunocompetent individuals with negative IGRAs is very unlikely. IGRAs may therefore be used in this context.
- It should be noted that, especially in risk groups and specific situations, a negative IGRA does not rule out LTBI.

### 3.2.8 Polymerase chain reaction test

*PCR.* The TB PCR assay on either endoscopic or surgical biopsy specimens from patients with ITB has been found to have a high level of accuracy for diagnosing ITB, with a specificity of up to 95% and an accuracy of 82.6% [17].

- A 2017 meta-analysis concluded that PCR for MTB is a promising and highly specific diagnostic method for distinguishing between ITB and CD. However, negative results cannot exclude ITB, due to the low sensitivity of the test [43].
- PCR testing in ascitic fluid may be useful in peritoneal tuberculosis [29].

### 3.2.9 Tuberculin skin test

*PPD.* Purified protein derivative (PPD) is an advanced version of the tuberculin skin test (TST). It is based on protein components from culture filtrates of MTB and is used to diagnose (latent) TB infection.

- Intradermal injection of 0.1 mL of PPD should be read after 48–72 hours.
- If the first test is negative, retesting may be done after 1–3 weeks.
- PPD testing is positive in approximately 70% of patients, but a negative result does not exclude the disease.

A false-negative PPD reaction may be secondary to:

- Cytokines initiated during active disease.
- Anergy due to another condition causing immune compromise—such as HIV and other viral infections.
- Severe, i.e. disseminated, TB.
- All immunosuppressive therapy.
- Poor nutrition.

Table **5** Correlation between the purified protein derivative (PPD) reaction in millimeters and patient risk categories [15]

| Reaction | Consider PPD positive in: |
|---|---|
| 5 mm | • High-risk patients |
| 10 mm | • High-risk patients<br>• Patients with a high probability of recent infection<br>• If any of the following risk factors are present:<br>— Recent immigration from TB-endemic countries<br>— HIV-negative intravenous drug users<br>— Residents of hospitals, nursing homes, prisons, mental-health facilities, homeless shelters<br>— Health-care workers, laboratory personnel<br>— All children < 4 years old<br>— Any child exposed to adults who are at high risk for TB |
| 15 mm | • Low-risk populations:<br>— Patients tested as part of routine screening, with no risk factors or known exposure |

The diagnostic value of the PPD skin test for ITB is uncertain, and results are influenced according to the prevalence of TB in the population that is being tested [13,15,17]:

- A positive test in a high-prevalence community (> 20 per 100,000/year) is more likely to indicate a true TB infection, and it may be false-positive in a low-prevalence community (< 10 per 100,000/year).
- In areas of the world in which the BCG vaccination is still given, the false-positive rate of the TST is very high.
- The diagnostic value is also limited in patients with a weakened immune response at the time of PPD reading. This may be due to:
  — HIV infection
  — Primary and disseminated TB
  — Use of corticosteroids or immunomodulating drugs

### 3.2.10 Adenosine deaminase

*Adenosine deaminase* (ADA) is a reliable enzyme marker for tuberculous ascites. An ADA cut-off value of between 36 and 40 IU/L has a high sensitivity (100%) and specificity (97%) for diagnosing peritoneal tuberculosis [23,44].

- Ascitic ADA activity assessment is a relatively sensitive and specific test for the diagnosis of tuberculous peritonitis—the pooled sensitivity and specificity figures for diagnosing tuberculous peritonitis were 0.93 (95% CI, 0.89 to 0.95) and 0.96 (95% CI, 0.94 to 0.97), respectively, in a meta-analysis of 16 studies [45], and 0.93 and 0.94, respectively, in a study with data from 17 studies including 1797 patients [46].

- In Western countries, particularly in high-risk patient groups, this testing procedure may also supersede invasive studies.
- An ADA activity assay may not be generally available in medical centers.
- Particularly in underdeveloped areas, where laparoscopy may not be available and where TB is endemic, measuring ascites adenosine deaminase (ADA) levels is an important tool for the diagnosis of tuberculous peritonitis [8].

#### 3.2.11 TB diagnostic technologies endorsed by WHO

**Molecular detection of TB and drug resistance**

- Xpert MTB/RIF Ultra for detecting TB and rifampicin resistance in pulmonary, extrapulmonary, and pediatric samples (Cepheid, Sunnyvale, California, USA)
- Line probe assays for detecting *Mycobacterium tuberculosis* (MTB), isoniazid resistance, and rifampicin resistance in acid-fast bacilli smear positive sputum or MTB cultures (FL-LPA) (Hain Lifescience GmbH, Nehren, Germany and Nipro, Osaka, Japan)
- Line probe assays for detecting resistance to fluoroquinolones and second-line injectable agents (SL-LPA) (Hain Lifescience GmbH)
- TB LAMP for detecting TB (Eiken Chemical Co., Ltd., Tokyo, Japan)

**Nonmolecular technologies**

- Alere Determine TB-LAM (Alere International Ltd., Galway, Ireland)—for detecting TB in people who are seriously ill with HIV
- Interferon-gamma release assay (IGRA) for diagnosing latent TB infection (LTBI) (Oxford Immunotec, Abingdon, UK; Qiagen, Germantown, Maryland, USA)

**Culture-based technologies**

- Commercial liquid culture systems and rapid speciation
- Culture-based phenotypic drug susceptibility testing (DST) using 1% critical proportion in LJ,7H10,7H11 and mycobacterial growth indicator tube (MGIT) media

**Microscopy**

- Light and light-emitting diode microscopy (diagnosis and treatment monitoring) [12]

## 3.3 Differential diagnosis

### 3.3.1 Peritoneal tuberculosis

Differential diagnosis based on lesion type [14]:

- *Ascites:* causes of exudative ascites—e.g., carcinomatous ascites, Budd–Chiari syndrome
- *Tubercles:* carcinomatosis

Table **6** Differential diagnosis for low serum-ascites albumin gradient (SAAG) < 11 g/L or exudative ascites [23,47]

| Malignancy | Infectious |
|---|---|
| • Peritoneal carcinomatosis | • Secondary bacterial peritonitis |
| • Hepatocellular carcinoma | • Tuberculous peritonitis |
| • Mesothelioma | • Chlamydia |
| • Metastatic liver disease | |
| • Other intra-abdominal malignancies | |

### 3.3.2 Intestinal tuberculosis

Differential diagnosis based on lesion type [14]:

- *Ulcerative:* Crohn's disease, ulcerative jejunitis (refractory celiac disease type 2), tropical sprue, immunoproliferative small-intestinal disease
- *Strictures:* Crohn's disease, malignancy (adenocarcinoma and lymphoma), ischemic
- *Hypertrophic:* carcinoma of the cecum, appendicular lump, amebic granuloma, actinomycosis, Crohn's disease
- *Perforations:* typhoid, Crohn's disease
- *Fistulas:* Crohn's disease

### 3.3.3 TB and Crohn's disease

Crohn's disease (CD) is an idiopathic inflammatory disease with a definite genetic background and modified by multiple environmental factors [17]. The diagnosis of CD is based on a combination of clinical features, endoscopic characteristics, and histological characteristics [26].

Along with the incidence of TB, the incidence of CD in areas that are endemic for TB has also increased [17,48,49].

- A study in Saudi Arabia reported that the mean annual incidence of CD over two decades rose from 0.32/100,000 to 1.66/100,000; similar results were found in the pediatric population in the same area.
- In a Lebanese study covering the years 2000–2004, the mean annual incidence was found to be 1.4/100,000; similar findings were also observed in Iran, Asia, and South Africa.
- In an Asia–Pacific Crohn's and Colitis Epidemiology Study, a large-scale population-based study in eight countries across Asia and in Australia, the crude annual overall incidence values for individuals were:
  — For Asia: 1.37/100,000 for inflammatory bowel disease (IBD), 0.76/100,000 for ulcerative colitis (UC), 0.54/100,000 for CD, and 0.07/100,000 for IBD-undetermined.
  — For Australia: 23.67/100,000 for IBD, 7.33/100,000 for UC, 14.00/100,000 for CD, and 2.33/100,000 for IBD-undetermined.
  — China had the highest incidence of IBD in Asia, at 3.44/100,000.
  — The ratios of UC to CD were 2.0 in Asia and 0.5 in Australia [48].

Table **7** Features of Crohn's disease versus intestinal tuberculosis [11,17,30,50]

| Indicators for CD diagnosis | Indicators for ITB diagnosis |
|---|---|
| • Younger age<br>• Relapses and remissions<br>• Shorter duration of symptoms | • Chronic, continuous disease course |
| • Aphthoid ulceration | • High-swinging fever (> 38.5 °C) in the absence of any intra-abdominal abscess (although fever is seen in both CD and ITB) |
| • Perianal disease<br>• Enteric fistulas<br>• Extraintestinal manifestations of CD (although TB involvement of the lower limb joints, skin, eye and liver may mimic extraintestinal CD)<br>• Bleeding per rectum<br>• Diarrhea | • Peritoneal involvement with ascites (but this is often absent and not very discriminatory) |
| • Negative tissue TB PCR and culture | • Positive tissue TB PCR and culture<br>• IGRAs and/or PPD test strongly positive |
| • *Radiological features:* long-segment strictures, multiple sites involved, comb sign, perianal disease | • *Radiological features:* short strictures, deformed ileocecal valve, lymphadenopathy with hypodense centers, thickened peritoneum |
| • *Endoscopic features:* longitudinal ulcers, aphthous ulcers, cobblestoning, perianal disease; long segment of ileal involvement with sparing of ileocecal valve | • *Endoscopic features:* transverse ulcers, nodules, scars, short-segment strictures; ileocecal valve almost always diseased—fixed patulous ileocecal valve is a very typical sign for ITB |
| • *Histological features:* granulomas (noncaseating, small, loss, and infrequent); focally enhanced colitis; mucosal architectural loss present even distant from granulomas | • *Histological features:* granulomas (caseating, large, confluent, and more in number); mucosal architectural loss only close to granulomas; prominent submucosal inflammation |

CD, Crohn's disease; IGRA, interferon-gamma release assay; ITB, intestinal tuberculosis; PCR, polymerase chain reaction; PPD, purified protein derivative.

IBD is an important differential diagnosis in both developed and developing countries. In developing countries with endemic TB with high rates of latent infection, testing otherwise healthy individuals for "exposure" is not appropriate.

### 3.3.4 Other diagnoses to consider

- Pseudomyxoma peritonei
- Peritoneal lymphomatosis
- Diffuse peritoneal leiomyomatosis
- Benign splenosis

# 4 Management

## 4.1 Drug treatment for extrapulmonary TB

Patients with abdominal TB should receive a full course of antitubercular therapy.

A 2-month course of treatment as detailed in Table **8** is currently recommended for uncomplicated ITB. Longer treatment should be avoided, as it is associated with poor compliance and an increased risk of side effects of potentially toxic drugs.

Table **8** Recommended treatment regimen for uncomplicated ITB [13,38]

| Course duration | Number of drugs | Drugs |
|---|---|---|
| 2 months | Four drugs | • Rifampicin<br>• Isoniazid<br>• Ethambutol<br>• Pyrazinamide |
| 4 months | Two drugs | • Rifampicin<br>• Isoniazid |
| | In cases of recurrent disease, drug resistance, or serious illness | Continue ethambutol |

Table **9** Antituberculosis drugs

| First-line drugs | Second-line drugs | WHO classification | |
|---|---|---|---|
| Isoniazid | Streptomycin | Group 1 | Isoniazid, rifampicin, ethambutol, pyrazinamide |
| Rifampicin (rifampin) | Cycloserine | Group 2 | Injectables: streptomycin, kanamycin, amikacin |
| Pyrazinamide | p-Aminosalicylic acid | Group 3 | Quinolones—e.g., levofloxacin, moxifloxacin |
| Ethambutol | Ethionamide | Group 4 | Other bacteriostatic second-line drugs—e.g., ethionamide, prothionamide, cycloserine, para-aminosalicylic acid (PAS) |
| Rifabutin* | Amikacin or kanamycin* | Group 5 | Agents with an unclear role—e.g., linezolid, amoxicillin–clavulanate , imipenem-cilastatin, high-dose isoniazid (INH) |
| Rifapentine | Capreomycin | | |
| | Levofloxacin* | | |
| | Moxifloxacin* | | |
| | Gatifloxacin* | | |

*Sources:* Centers for Disease Control, World Health Organization.

* Not approved by the United States Food and Drug Administration (FDA) for use in TB treatment.

*Notes* [5,8]

• Extrapulmonary TB should be treated using the same antituberculous drug regimens as pulmonary TB disease. Regimens of 6, 9, and 18–24 months are all effective for extrapulmonary tuberculosis.

• A Cochrane review found no evidence to suggest that 6-month treatment regimens are inadequate for treating people who have intestinal and peritoneal TB, but the numbers are small [5].

• Anti-TB treatment should be started immediately (irrespective of the CD4 count in case of HIV/TB co-infection).

• Standard therapy of at least 9 months' duration is also effective in most AIDS patients who are started on appropriate treatment in a timely fashion and who are compliant.

• The potential for multidrug resistance needs to be kept in mind and accounted for.

• Treatment of tuberculosis in AIDS patients is the same as in patients without HIV infection, but multidrug-resistant tuberculosis is more common in patients with AIDS.

## 4.2 Side effects

**Hepatotoxicity may be caused by isoniazid (INH), rifampicin (RIF), or pyrazinamide (PZA)**

- Drug-induced hepatitis may be asymptomatic or symptomatic [15].
- It is defined in asymptomatic patients as a serum aspartate transaminase (AST) level of five times the upper limit of normal.
- It is defined in symptomatic patients (most commonly presenting with abdominal pain, nausea, vomiting) as an AST of three times the upper limit of normal.
- If a patient presents to the emergency department with a significant elevation of AST, the medication should be discontinued.

**Monitoring for drug-induced hepatotoxicity (DIH) or drug-induced liver injury (DILI)** [11]

- Patients receiving antituberculous therapy with first-line drugs should undergo baseline measurement of hepatic enzymes (transaminases, bilirubin, and alkaline phosphatase).
- Acute viral hepatitis should be ruled out by testing for hepatitis B and C in patients with epidemiologic risk factors.
- Repeated hepatic enzyme measurements—every 2 weeks for the first 3 months, then monthly—are recommended in the following situations (not necessary for patients with normal baseline results):
  — Abnormal baseline results
  — Suspected DIH reaction
  — Liver disease (e.g., hepatitis B or C, alcohol abuse)
  — Pregnancy and the first 3 months postpartum
  — Combination therapy including pyrazinamide in the continuation phase
- Symptoms of hepatic toxicity include: anorexia, nausea, vomiting, dark urine, icterus, rash, pruritus, fatigue, fever, abdominal discomfort (particularly right upper quadrant discomfort), easy bruising or bleeding, and arthralgias.
  — Patients must be educated about the symptoms.
  — Patients should be directly questioned about these symptoms at monthly visits.
  — Patients should immediately report any signs or symptoms that occur in the interval between the monthly visits.

- Positive predictors of DIH:
  — Age > 35 years (with a fourfold increase in the risk for developing TB DILI)
  — Female gender
  — Hepatitis B (fourfold increase in the risk for $HB_sAg$ carriers versus noncarriers)
  — Hepatitis C (fivefold increase in risk)
  — Alcohol intake
  — Cirrhosis
  — Nutrition: mid arm circumference < 20 cm, baseline hypoalbuminemia
  — Genetic polymorphism (this is not tested to detect the risk of hepatotoxicity in developing countries)

Other medication side effects include gastrointestinal symptoms, rash, and drug–drug interactions.

## 4.3 Antibacterial resistance

Multidrug resistance (MDR) has been observed in 2.4–13.2% of strains of MTB isolated from newly diagnosed pulmonary TB patients and in 17.4–25.5% of previously treated patients. Extensive drug resistance (XDR) is found almost exclusively in previously treated patients and accounts for about 6% of MDR-TB.

**WHO shorter MDR-TB regimen:**

- Kanamycin (an injectable agent), moxifloxacin, prothionamide, clofazimine, isoniazid, pyrazinamide and ethambutol, given together in an initial phase of 4 months (with the option of extending to 6 months if the patient is still positive on a sputum smear at the end of month 4).
- Followed by an intensive phase of 5 months of treatment with four of the medicines (moxifloxacin, clofazimine, pyrazinamide, and ethambutol).
- Medicines are taken once per day, all days of the week.
- If the intensive phase is prolonged, the injectable agent is only given three times a week after the fourth month.

Table **10** WHO dosage scheme for shorter MDR-TB regimen [51]

| | Weight group | | |
|---|---|---|---|
| **Drug** | **< 30 kg** | **30–50 kg** | **> 50 kg** |
| Moxifloxacin | 400 mg | 600 mg | 800 mg |
| Clofazimine | 50 mg | 100 mg | 100 mg |
| Ethambutol | 800 mg | 800 mg | 1200 mg |
| Pyrazinamide | 1000 mg | 1500 mg | 2000 mg |
| Isoniazid | 300 mg | 400 mg | 600 mg |
| Prothionamide | 250 mg | 500 mg | 750 mg |
| Kanamycin | 15 mg per kg body weight (max. dose 1000 mg)<br>For adults > 59 years of age: reduce dose to 10 mg/kg (max. dose 750 mg) | | |

## 4.4 Empirical treatment

Empirical antituberculous drug treatment for 2–3 months may be considered appropriate in countries with a high prevalence of abdominal TB and if the clinical features are compatible—i.e., the clinical, radiographic, and endoscopic data are consistent with the diagnosis of abdominal TB and if other common diseases such as cancer, nonspecific inflammatory bowel disease, and other specific infections can be adequately ruled out [13].

The diagnosis of tuberculous enteritis can be taken as highly probable if the patient responds to treatment and if no relapse occurs at the end of follow-up [8].

Monitoring of the response should be carried out weekly for 4–6 weeks:

- Resolution of symptoms
- Weight gain
- Improving hemoglobin and a fall in C-reactive protein (CRP) levels are more sensitive than a fall in the erythrocyte sedimentation rate (ESR) in determining the response to TB therapy [52].

However, it is recommended that a TB diagnosis should be established before commencing treatment, for the following reasons [11,17]:

- A partial response to antitubercular therapy in patients with Crohn's disease and emergence of MDR tuberculosis restricts the usefulness of the response to ATT as a way of establishing the diagnosis of tuberculosis.
- Anti-TB treatment may have significant side effects and morbidity.
- Patients with CD who are treated with immunosuppressants have a higher risk of acquiring infections, including TB—this can lead to coexistence of two diseases.

When laparoscopy is not available or not affordable, and if patients are inoperable, ascitic ADA testing can be crucial for making a quick diagnosis of peritoneal tuberculosis and starting empirical anti-tuberculosis drugs.

In patients with a high index of suspicion of peritoneal tuberculosis and ADA > 30 IU, antituberculosis treatment can be started.

## 4.5 TB and Crohn's disease

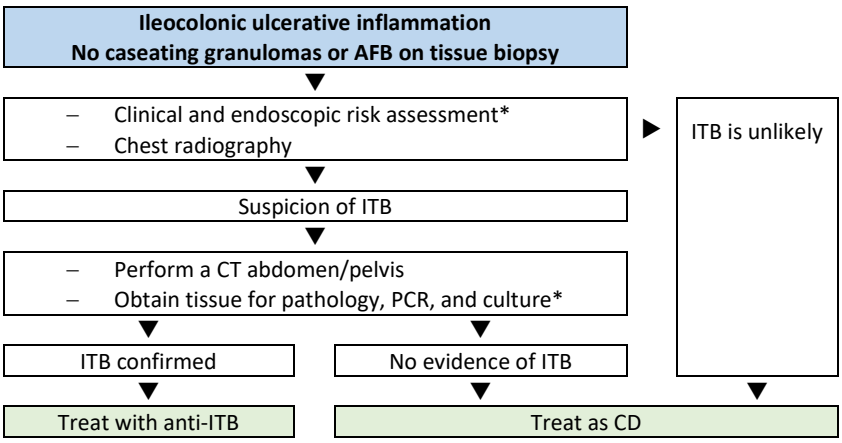


Fig. **2** Algorithm for the management of Crohn's disease (CD) versus intestinal tuberculosis (ITB) [17]. AFB, acid-fast bacillus; PCR, polymerase chain reaction.

*Notes:*
• If PCR is not available, consider empirical antitubercular therapy.
• If the culture is positive, continue treatment, if negative consider Crohn's disease.
* Clinical risk assessment includes consideration of a history of previous TB originating from a high-prevalence area and high swinging fever, in the absence of an intra-abdominal abscess.

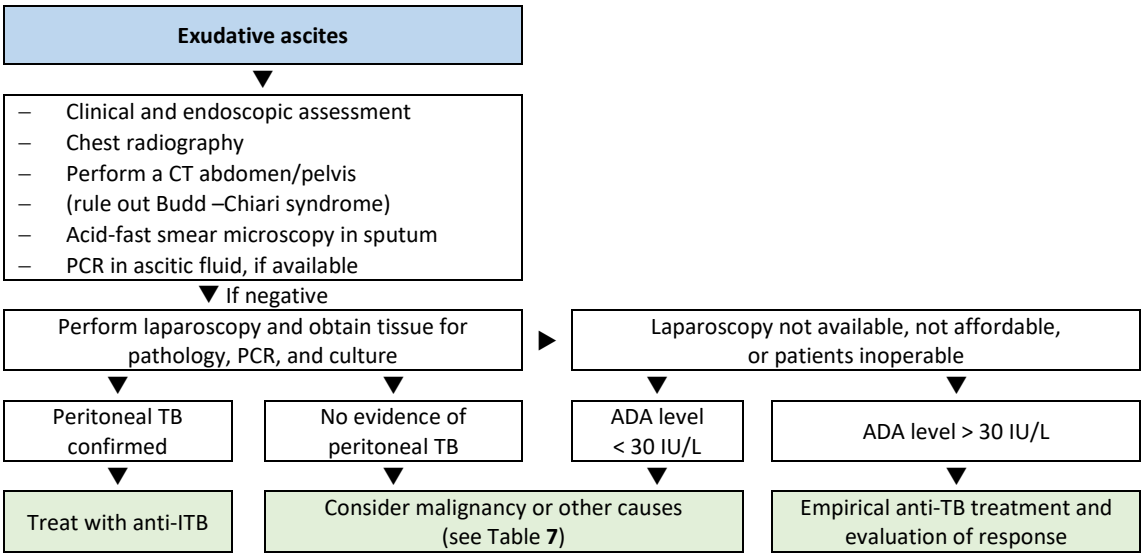


Fig. **3** Algorithm for the management of exudative ascites.
ADA, adenosine deaminase; CT, computed tomography; ITB, intestinal tuberculosis; PCR, polymerase chain reaction.
*Notes:*
• If PCR is not available and there is no evidence of peritoneal tuberculosis in a biopsy, consider empirical antitubercular therapy and wait for the culture results.
• If the culture is positive, continue treatment; if negative, consider Crohn's disease (although ascites is much less common in CD or any other cause of ascites).
• Adenosine deaminase (ADA) activity is increased in tuberculosis, liver disease, and certain malignancies (among other conditions).

## 4.6 Surgical treatment

Surgical intervention is reserved for complications—fibrosis, strictures, and acute abdomen—or when there is uncertainty in the diagnosis.

Table **11** Abdominal tuberculosis and surgery [14]

| Site | Signs/symptoms | Suggested treatment |
|---|---|---|
| Any site | Acute abdomen | Emergency surgery |
| Intestinal | Ulcerative | Anti-TB treatment |
| | Strictural | Strictureplasty, resection |
| | Hypertrophic | Resection |
| Peritoneal<br>Lymph nodes | Ascitic, adhesive | Anti-TB treatment |

# 5 Appendix

## 5.1 Abbreviations

Table **12** Abbreviations used in this WGO guideline

| | |
|---|---|
| ADA | adenosine deaminase |
| AFB | acid-fast bacillus |
| ATT | antitubercular therapy |
| BCG | bacille Calmette–Guérin |
| CD | Crohn's disease |
| CRP | C-reactive protein |
| CT | computed tomography |
| DIH | drug-induced hepatotoxicity |
| DILI | drug-induced liver injury |
| DST | drug susceptibility testing |
| ECCO | European Crohn's and Colitis Organization |
| ECDC | European Centre for Disease Prevention and Control |
| EPTB | extrapulmonary tuberculosis |
| ESR | erythrocyte sedimentation rate |
| EUS | endoscopic ultrasonography |
| FDA | Food and Drug Administration |
| $HB_sAg$ | hepatitis B surface antigen |
| HIV | human immunodeficiency virus |
| IBD | inflammatory bowel disease |
| IGRA | interferon-gamma release assay |
| INH | isoniazid |
| ITB | intestinal tuberculosis |
| LNN | lymph-node necrosis |
| LTBI | latent tuberculosis infection |
| MDR-TB | multidrug-resistant tuberculosis |
| MGIT | mycobacterial growth indicator tube |
| MRI | magnetic resonance imaging |
| MTB | *Mycobacterium tuberculosis* |
| NPV | negative predictive value |
| PCR | polymerase chain reaction |
| PPD | purified protein derivative |
| PPV | positive predictive value |
| PZA | pyrazinamide |

| | |
|---|---|
| RIF | rifampicin (International Nonproprietary Name; U.S. Adopted Name rifampin) |
| SAAG | serum-ascites albumin gradient |
| TB | tuberculosis |
| TNF | tumor necrosis factor |
| TST | tuberculin skin test |
| UC | ulcerative colitis |
| WHO | World Health Organization |
| XDR-TB | extensively drug-resistant tuberculosis |

## 5.2 Guidelines on tuberculosis and gastrointestinal disease

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