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REVIEW ARTICLE

Evidence-based approach to diagnosis and management of abdominal tuberculosis

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Abstract

Abdominal tuberculosis is an ancient problem with modern nuances in diagnosis and management. The two major forms are tuberculous peritonitis and gastrointestinal tuberculosis (GITB), while the less frequent forms are esophageal, gastroduodenal, pancreatic, hepatic, gallbladder and biliary tuberculosis. The clinicians need to discriminate the disease from the close mimics: peritoneal carcinomatosis closely mimics peritoneal tuberculosis, while Crohn's disease closely mimics intestinal tuberculosis. Imaging modalities (ultrasound, computed tomography, magnetic resonance imaging and occasionally positron emission tomography) guide the line of evaluation. Research in diagnostics (imaging and endoscopy) has helped in the better acquisition of tissue for histological and microbiological tests. Although point-of-care polymerase chain reaction–based tests (e.g. Xpert Mtb/Rif) may provide a quick diagnosis, these have low sensitivity. In such situations, ancillary investigations such as ascitic adenosine deaminase and histological clues (granulomas, caseating necrosis, ulcers lined by histiocytes) may provide some specificity to the diagnosis. A diagnostic trial of antitubercular therapy (ATT) may be considered if all diagnostic armamentaria fail to clinch the diagnosis, especially in TB-endemic regions. Objective evaluation with clear endpoints of response is mandatory in such situations. Early mucosal response (healing of ulcers at two months) and resolution of ascites are objective criteria for early response assessment and should be sought at two months. Biomarkers, especially fecal calprotectin for intestinal tuberculosis, have also shown promise. For most forms of abdominal tuberculosis, six months of ATT is sufficient. Sequelae of GITB may require endoscopic balloon dilatation for intestinal strictures or surgical intervention for recurrent intestinal obstruction, perforation or massive bleeding.

Keywords Abdominal tuberculosis · AFB · Ascites · Colonoscopy · Culture · Extrapulmonary tuberculosis · Gastrointestinal tuberculosis · Intestinal tuberculosis · Mycobacterium tuberculosis · PCR · Pancreatic tuberculosis · Peritoneal tuberculosis · Surgery · Tuberculous peritonitis · Xpert

Introduction

Infection with *Mycobacterium tuberculosis* lasts a lifetime and the organism infects almost a quarter of the world population that remains at the risk of advancing to active disease [1, 2]. Tuberculosis affects nearly 10 million people and leads to death in more than a million people annually, despite being a preventable and curable disease [2]. It primarily involves the lung, but the incidence of extrapulmonary tuberculosis (EPTB) is around 15% globally. Abdominal TB is among the common sites of extrapulmonary involvement, where it tends to involve the gastrointestinal tract, peritoneum, lymph nodes and solid organs in that order. The diagnosis and management of abdominal TB are challenging: the disease is usually paucibacillary with a low yield of microbiological tests and it mimics many conditions closely, resulting in diagnostic confusion [3, 4]. In certain cases, relatively non-specific parameters such as ascitic fluid adenosine deaminase levels are utilized for diagnosis [5]. When the diagnosis remains unclear even after all these modalities, a therapeutic trial with antitubercular therapy (ATT) is often started in TB endemic regions and the response to the therapy is assessed. Since the disease is primarily a concern in the less developed world, the development of evidence-based diagnosis and treatment has lagged.

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A recent survey of clinicians suggested significant variations in clinical practice with respect to the diagnostic modalities, treatment duration and follow-up modalities in abdominal TB [6]. Therefore, the present review aims at providing an evidence-based summary to inform clinical practice for abdominal TB. Because gastrointestinal tuberculosis (GITB, also termed intestinal TB) and tuberculous peritonitis (TBP, also termed peritoneal tuberculosis [PTB]) are the most frequent clinical problems, the review is largely focused on these two entities.

Methods

Although the present review is a narrative review, a search of two databases, Pubmed and Embase, was performed on December 1, 2022, to inform the review. We used MESH words and free terms to search for Abdominal Tuberculosis OR Peritoneal Tuberculosis OR Tuberculous peritonitis OR Gastrointestinal Tuberculosis OR Intestinal Tuberculosis. We aimed at providing evidence-based recommendations regarding several contentious areas in the diagnosis and management of abdominal TB, including evaluation pathways, diagnostic armamentarium to be used (standard culture or liquid culture, number/amount of tissue or fluid, which polymerase chain reaction (PCR)–based tests, whether to use adenosine deaminase and the cut-off for PTB) and treatment strategies (duration of ATT, additional role of ancillary therapies such as steroids, use of diagnostic trial and the duration of such a trial, appropriate methods of assessment after a diagnostic trial of ATT). Wherever systematic reviews (Tables 1 and 2) or randomized studies were available, we used these to summarize the management recommendations [7–24]. Where systematic reviews or randomized clinical trials (RCTs) were not available, we used observational studies to suggest an appropriate clinical approach. We also identify advances in the field that are likely to be useful in clinical practice in the coming times, lacunae in the current literature and avenues for future research.

Epidemiology of abdominal tuberculosis

The number of cases of abdominal TB as a fraction of all EPTB cases has been reported to vary from 2.7% to 21% [25, 26]. In a study from three states in India and based on the national tuberculosis program, abdominal TB constituted 12.8% of all EPTB cases [26]. Lower treatment completion rates and worse outcomes have been reported in abdominal TB [26, 27]. Among patients with abdominal TB, both GITB and tuberculous peritonitis have been reported as common sites [28, 29]. Because of a possible selection bias, PTB being easier to diagnose based on abdominal paracentesis, GITB is often reported as the commonest form of abdominal TB in most reports from tertiary care centers [25].

Certain comorbidities, especially chronic liver disease, specifically increase the predisposition to abdominal/PTB [30]. Additional risk factors for developing abdominal TB include younger age, female gender, Asian ethnicity, human immunodeficiency virus (HIV) coinfection, immunosuppression, diabetes mellitus and peritoneal dialysis [30–32].

Clinical presentation

In a systematic review on tuberculous peritonitis, abdominal pain (65%), fever (59%), weight loss (61%), diarrhea (21%) and constipation (11%) were the most frequently reported symptoms [32]. The presence of ascites (73%), abdominal tenderness (48%), hepatomegaly (28%) and splenomegaly (14%) were the most frequent clinical findings (16,197,489). Constitutional symptoms occur in half of the patients. Because of the non-specific nature of the symptoms, the diagnosis can be delayed (7–24 weeks from the onset of symptoms) [33]. Although less frequent than GITB, TBP may also have features of intestinal obstruction, especially in the presence of adhesions, peritoneal fibrosis or sclerosing encapsulating peritonitis (i.e. abdominal cocoon) [34].

The clinical presentation of intestinal TB is dominated by abdominal pain (30% to 88%), fever (21% to 73%), diarrhea (5% to 47%), loss of appetite (30% to 90%), loss of weight (8% to 80%), constipation (7% to 24%), and hematochezia (5% to 15%). Some patients may present with intestinal obstruction (3% to 36%) [35]. Concomitant or past pulmonary TB could be present in up to 25% of cases [36]. The rising incidence of inflammatory bowel disease (IBD) in India does not seem to have reduced the numbers of GITB. Hence distinguishing the two continues to be a major challenge [37].

Case definitions

A large number of case definitions and classifications for abdominal TB are in vogue and are based on clinical presentation, morphological patterns, basis of diagnosis and response to ATT (Fig. 1). Traditionally, Paustian criteria were proposed but are impractical in the modern era, as they rely on surgical specimens and animal inoculation. Logan proposed a response assessment that continues to be used to date for diagnosing GITB [38]. The cases of abdominal TB could be defined on the basis of clinical presentation—pain (strictures, hypertrophic lesions) or diarrhea (diffuse ulcers) for intestinal TB and pain predominant (peritoneal adhesions

Table 1 Summary of available evidence based on the systematic reviews on tuberculous peritonitis

Research query	Reference	Evidence base	Comparison	Results	Interpretation
What are the imaging features in CT to differentiate TBP from peritoneal carcinomatosis?	Chen et al. 2020 [7]	4 studies, 483 participants	Smooth peritoneal thickening	The specificity and sensitivity of 84% and 59%, respectively	No single finding seems adequately sensitive and specific
	Chen et al. 2020 [7]	5 studies, 605 participants	Ascites	The sensitivity and specificity of 50% and 58%, respectively	
	Chen et al. 2020 [7]	3 studies, 313 participants	Lymph node necrosis	The sensitivity and specificity and 21% and 100%, respectively	
What is the diagnostic accuracy of (IFN-γ level testing for the diagnosis of tuberculous peritonitis?	Su et al. 2013 [8]	6 studies	IFN-γ level in diagnosing TB peritonitis	The sensitivity was 0.93 (95% CI: 0.87–0.97) and specificity, 0.99 (95% CI: 0.97–1.00)	Similar performance as ascitic adenosine deaminase Unclear if any incremental benefit
What is the diagnostic accuracy of adenosine deaminase in peritoneal fluid for the diagnosis of tuberculous peritonitis?	Riquelme et al. 2006 [9]	4 studies, 264 participants	Using ADA cut-off 36–40 IU/L in peritoneal fluid to diagnose peritoneal TB	The pooled sensitivity and specificity are 100% and 97%, respectively	Variable cut-off and methods used in participating studies Good sensitivity and specificity for the diagnosis
	Shen et al. 2013 [10]	16 studies, 1574 participants	ADA in peritoneal fluid	The pooled sensitivity was 0.93 (95% CI: 0.89–0.95), specificity was 0.96 (95% CI: 0.94–0.97)	
	Tao et al. 2014 [11]	17 studies, 1797 subjects	Using ADA 35 IU/L to diagnose peritoneal TB against CRS	The sensitivity and specificity are 93% and 94%, respectively	
	Zhou et al. 2022 [12]	24 studies, 3044 participants	Variable usually composite reference	Pooled sensitivity of 93% (95% CI: 0.89–0.95) and 95% (95% CI: 0.93–0.96), respectively	
What is the diagnostic accuracy of T-SPOT testing for the diagnosis of tuberculous peritonitis?	Luo et al. 2020 [13]	8 studies, 786 participants	T-SPOT in peripheral blood compared to composite reference standard	Pooled sensitivity and specificity of PB T-SPOT in diagnosing peritoneal TB were 0.91 (95% CI: 0.88–0.94) and 0.78 (95% CI: 0.73–0.81)	Poor specificity limits use as many positive cases would have alternative diagnosis
	Luo et al. 2020 [13]	7 studies, 423 participants	T-SPOT in peritoneal fluid compared to composite reference standard	The pooled sensitivity and specificity of PF T-SPOT are 0.90 (95% CI: 0.85–0.94) and 0.78 (95% CI: 0.72–0.83)	
What is the diagnostic accuracy of Xpert MTB/RIF testing in ascitic fluid for the diagnosis of tuberculous peritonitis?	Kohli et al. 2021 [14]	13 studies with 580 participants	Xpert Mtb Rif against mycobacterial culture from ascitic fluid	Pooled sensitivity and specificity 59.1% (42.1–76.2) and 97.6% (95.4–98.9), respectively	Xpert Mtb/Rif provides a quick diagnosis with excellent specificity. However, low sensitivity means a significant number of patients will be missed
	Sharma et al. 2021 [15]	18 studies, 1099 samples	Xpert Mtb Rif against mycobacterial culture from ascitic fluid	Pooled sensitivity and specificity 64% (95% CI: 49–76%) and 97% (95–99), respectively	
		8 studies, 634 samples	Xpert Mtb Rif in ascitic fluid compared to a composite reference standard	Pooled sensitivity and specificity: 30% (22–40%) and 100% (98–100%)	

Table 1 (continued)

Research query	Reference	Evidence base	Comparison	Results	Interpretation
What is the role of adjunctive steroids for treating tuberculous peritonitis?	Soni et al. 2019 [16]	3 studies, 108 participants	Adjunctive steroids with ATT compared to ATT alone	Adjunctive steroids used with ATT was more effective than compared with using ATT for the prevention of composite end point (RR: 0.15 [0.04, 0.62], $p = 0.008$), symptomatic stricture (RR: 0.15 [0.04–0.62] $p = 0.008$), and intestinal obstruction (RR: 0.18 [0.03–0.99] $p = 0.05$)	Poor quality of included studies only in the setting of peritoneal tuberculosis Limited generalizability Steroids should not be routinely used
What is the duration for which ATT must be used to achieve clinical cure?	Jullien et al. 2016 [17]	3 trials, 294 participants	Participants that achieved clinical cure on 6 months compared to 9 months of ATT	RR: 1.02, 95% CI: 0.97 to 1.08	Only one RCT included in systematic review included patients with TBP. However, combination of this trial and observational data suggests that 6 months of therapy is adequate

RR relative risk, *CT* computed tomography, *TBP* tuberculous peritonitis, *AFB acid* fast bacilli, *ADA* adenosine deaminase, *ATT* Antitubercular therapy, *PB* Peripheral blood, *PF* Peritoneal fluid, *CI* Confidence interval, *RCT* randomized controlled trial, *CI* confidence interval, *TB* tuberculosis, *IFN-γ* Interferon-gamma, *CRS* composite reference standard

or fibrosis) or distension predominant (ascites in PTB) for tuberculous peritonitis [39]. The morphological patterns have also been described for intestinal TB and tuberculous peritonitis, but an overlap among these patterns is well recognized. A systematic review of definitions of PTB identified that the classification into wet, dry and fibrotic forms is dogged by overlapping features and is better avoided [39]. Therefore, clinicians should largely follow a case definition that provides information regarding the confidence of diagnosis—a hierarchical strategy may be helpful and would largely be consistent with the definitions of INDEX-TB guidelines [40]. A microbiologically positive case would have the highest confidence in the diagnosis, while in the absence of microbiological positivity, a diagnosis of a clinically diagnosed case is made. It is important to recognize that all clinically diagnosed cases of abdominal TB are not equal: certain findings such as caseating granulomas or high ascitic adenosine deaminase levels may provide more certainty, while a diagnosis based on consistent clinical-radiological findings and exclusion of alternative diagnosis is much less secure. The confidence in the diagnosis has clinical relevance because the clinicians would need to follow patients with possible abdominal TB more closely and evaluate them for objective evidence of response to ATT. Figure 1 suggests a hierarchical approach to the diagnosis of abdominal TB based on confidence in the diagnosis.

Evaluation

Serum markers/IGRA

Interferon-gamma release assays (IGRAs) have emerged as an important tool for the diagnosis of latent TB infection. These have also been used for possible discrimination of abdominal TB from mimics like Crohn's disease or other causes of ascites. These are believed to be helpful as these are not impacted by Bacille Calmette-Guérin (BCG) vaccination.

In a meta-analysis of 12 studies, the diagnostic accuracy of peripheral blood (PB) T-SPOT and peritoneal fluid (PF) T-SPOT for TBP was evaluated. The pooled sensitivity and specificity of PB T-SPOT for diagnosing peritoneal TB were 91% and 78%, respectively, while the pooled positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 4.05 and 0.13, respectively. On the other hand, the pooled sensitivity, specificity, PLR and NLR of PF T-SPOT for TBP were 90%, 78%, 6.35, and 0.14, respectively. The results summarized that both PB T-SPOT and PF T-SPOT are sensitive for diagnosing TBP. Still, the unsatisfactory specificity of these two methods limits application as rule-in tests for peritoneal TB diagnosis [13] (Table 1). In another systematic

Table 2 Summary of available evidence based on the systematic reviews on gastrointestinal tuberculosis

Research Query	Reference	Evidence base	Comparison	Results	Interpretation
Accuracy of CT in differentiating ITB from CD	Kedia et al. 2017 [18]	6 studies, 638 patients	Necrotic lymph node	Pooled sensitivity of 23% (95% CI: 17–29%) and specificity of 100% (95% CI: 99–100%)	Necrotic lymph nodes very specific, but not sensitive for GITB. Important to recognize that necrotic lymph nodes could occur in other conditions such as malignancy
	Kedia et al. 2017 [18]	2 studies, 209 patients	Ileocecal involvement	The pooled sensitivity and specificity were 64% (95% CI: 53–74%) and 77% (95% CI: 68–84%), respectively	
What is the clinical usefulness of using IGRA in differentiating GITB from CD?	Chen et al. 2013 [19]	5 studies, 610 patients	Composite reference using multiple parameters	Pooled sensitivity and specificity: 74% (53–100%) and 87% (63–98%), respectively Diagnostic odds ratio (DOR) in differentiating ITB vs CD was 26.2	Inability to differentiate latent from active TB
	Ng et al. 2014 [20]	8 studies, 705 patients	Composite reference using multiple parameters	Pooled sensitivity and specificity 81% (75–86%) and 85% (81–89%), respectively	
	Xu et al. 2016 [21]	12 studies from Asia (Chinese)	Performance of IGRAs (QuantiFERON-TB Gold or T-SPOT.TB)	Pooled sensitivity and specificity 82.8% (78.4–86.6%) and 86.7% (83.2–89.6%), respectively	
What is the usefulness of ASCA in differentiating CD from ITB?	Ng et al. 2014 [20]	6 studies, 603 patients	Composite reference	Pooled sensitivity and specificity were 33% (27–38%) and 83% (77–88%), respectively	Indian studies do not suggest much benefit
What is the diagnostic accuracy of Xpert Mtb/Rif testing in intestinal tissue for the diagnosis intestinal tuberculosis?	Sharma et al. 2021 [15]	5 studies, 460 samples	Composite reference standard	Pooled sensitivity and specificity: 23% (16–32%) and 100% (52–100%), respectively	Poor sensitivity but excellent specificity. Good rule in test but a poor rule out test
What is the clinical usefulness of detecting MTB PCR (IS6110) in biopsy or fecal samples in differentiating GITB from CD?	Jin et al. 2017 [22]	9 studies, 709 patients	Composite reference	Pooled sensitivity and specificity: 47% (42–51%) and 95% (93–97%), respectively DOR of 21.92	Fair sensitivity and good specificity
What is the diagnostic accuracy of histological features in differentiating GITB and CD?	Du et al. 2014 [23]	9 studies, 692 patients	Caseation versus composite reference	Sensitivity: 21% (15–28%) Specificity: 100% (98–100%) DOR: 13.74	Some of the features are specific but have a low sensitivity
	Du et al. 2014 [23]	5 studies	Confluent granulomas	Specificity: 38% (30–47%) Sp: 99% (95–100%) DOR: 26.52	
	Du et al. 2014 [23]	3 studies	Ulcers lined by epithelioid histiocytes	Specificity: 41% (32–51%) Sp: 94% (88–98%) DOR: 13.17	

CT Computed tomography, *ITB* intestinal tuberculosis, *CD* Crohn's disease, *ASCA* anti-Saccharomyces cerevisiae antibody, *GITB* Gastrointestinal tuberculosis, *IGRA* Interferon gamma release assay; *MTB PCR* Mycobacterium tuberculosis-polymerase chain reaction test, *DOR* diagnostic odds ratio, *CI* confidence interval

	Gastrointestinal Tuberculosis	Peritoneal Tuberculosis
Clinical presentation	Pain dominant Diarrhea dominant	Pain dominant Distension dominant
Morphological	Ulcerative Hypertrophic Stricturing/ Stenotic Combination	Wet – ascitic Dry plastic Fibrotic fixed Cocoon
Diagnosis	Clinical diagnosed (Probable or Possible) Microbiologically diagnosed (Confirmed)	

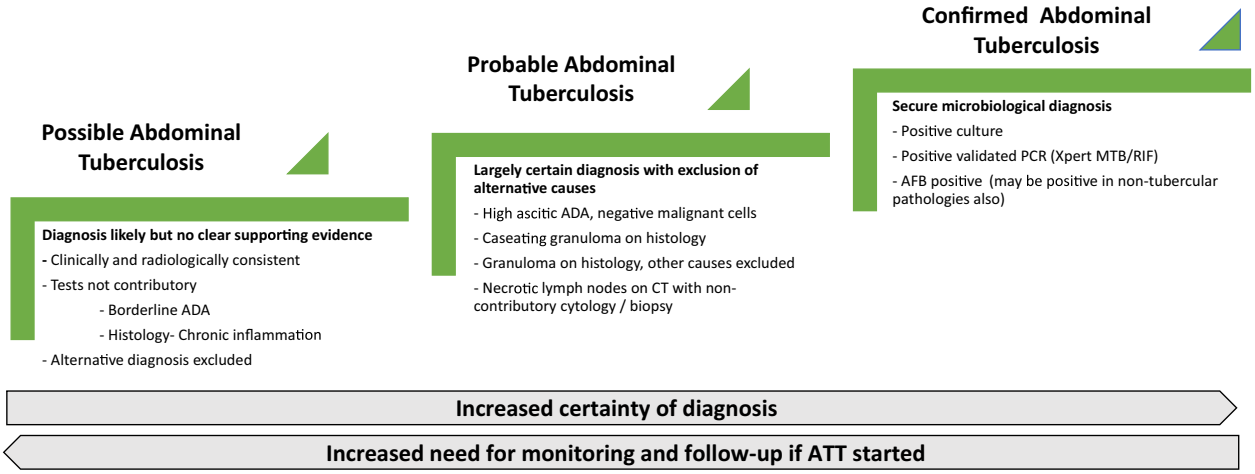

Fig. 1 Summary of case definitions and a hierarchical approach to defining an abdominal tuberculosis case. *ADA* adenosine deaminase, *CT* computed tomography, *PCR* polymerase chain reaction, *AFB* acid-fast bacilli

review, interferon-gamma levels in the ascitic fluid were reported to have an excellent sensitivity and specificity (93% and 99%, respectively), but the incremental values over ascitic ADA are uncertain [8].

IGRAs have also been evaluated in multiple studies as a diagnostic modality to discriminate GITB from Crohn's disease (CD). Three meta-analyses have been published (Table 2) [19–21]. In the most recent meta-analysis by Xu et al., 12 studies were included and a pooled sensitivity of 82.8% (78.4–86.6%) and a pooled specificity of 86.7% (83.2–89.6%) were reported [21]. The authors of these meta-analyses concluded that IGRA is a good supplementary method to discriminate between intestinal tuberculosis (ITB) and CD. Some other studies, however, report poor sensitivity and specificity and question the utility of this test [41].

There are certain caveats to the use of this test—in TB-endemic regions, patients with IBD would also be exposed to tuberculosis. They may have a positive IGRA, while many with disseminated TB or malnutrition may not demonstrate immune responsiveness on exposure to TB antigens. A recent report highlighted the value of quantitative measurements using enzyme-linked immunoassay (ELISA), suggesting that the levels of > 100 pg/mL had a higher sensitivity and specificity for discriminating ITB from CD [42]. With the available evidence, the role of IGRA in the diagnosis of active abdominal TB is unclear and should not be routinely done in TB-endemic regions to diagnose active TB. However, it may have a role in excluding TB if a diagnosis of CD is considered in TB-endemic settings, with the caveats already mentioned.

Imaging modalities

The initial imaging used for evaluation is often abdominal ultrasound (USG) which can help in the evaluation of lymphadenopathy, peritoneal or omental thickening, ascites, mesenteric changes and bowel wall thickening. The use of bowel ultrasound in the evaluation of strictures has been reported in the setting of IBD, although this is yet to be reported systematically in the setting of GITB [43]. Nevertheless, ultrasound provides a good initial evaluation in suspected abdominal TB cases and can also provide material for microbiological, cytological or histopathological evaluation [44]. In a systematic review on the utility of abdominal ultrasonography for the diagnosis of TB in the setting of HIV, the sensitivity and specificity for the diagnosis of abdominal TB were 63% and 68%, respectively, against a microbiological standard. These findings suggest that a negative ultrasound should not be used to exclude abdominal TB in HIV-positive individuals [24].

Computed tomography (CT) has emerged as an excellent tool for evaluating abdominal diseases because of its easy

availability and excellent resolution. It provides good visualization of both luminal and extraluminal findings [43]. A systematic review of six studies compared the yield of 17 CT findings in discriminating TBP from peritoneal carcinomatosis. The highest diagnostic accuracy for TBP was achieved by smooth peritoneal thickening (AUC: 0.83), with fairly good specificity (84%), but limited sensitivity (59%). The location and presence of ascites showed poor diagnostic accuracy (AUC: 0.63) because of both poor sensitivity (50%) and specificity (58%). Lymph node necrosis and calcification showed an impressive specificity (95% and 100%, respectively) but poor sensitivity (10% and 12%, respectively) [7].

Another systematic review of six studies with 612 patients assessed the role of various CT findings in the discrimination of GITB and CD. Certain findings such as necrotic lymph nodes (sensitivity: 23% and specificity: 100%) and ileocecal involvement (sensitivity: 64% and specificity: 77%) suggested the diagnosis of GITB. Other features including comb sign, skip lesions, asymmetric bowel involvement, mural stratification, long segment involvement, fibrofatty proliferation and left-sided colonic involvement were associated with a diagnosis of CD. However, none of these findings (except for necrotic lymph nodes) were pathognomonic of a particular diagnosis [18]. Certain other CT findings, which could suggest a diagnosis of abdominal TB, include the presence of pulmonary involvement (15% to 25% cases), omental line or rim (thick uniformly enhancing outer rim of thickened omentum) and low visceral fat to subcutaneous fat ratio (< 0.63) [36, 45, 46]. Concomitant genitourinary involvement, especially in females with salpingitis, hydrosalpinx, adnexal lesions and tubo-ovarian masses, could suggest underlying TB [47]. USG or CT-guided fine-needle aspiration cytology or biopsy provides an opportunity to clinch a microbiological or cytological/histological diagnosis from extraintestinal lesions such as lymph nodes, peritoneal or omental deposits or thickening [44, 48].

Advances in MRI could further improve diagnostics and follow-up. Magnetic resonance enterography (MRE) has been shown to identify more strictures than barium studies [49]. Also, diffusion-weighted imaging and apparent diffusion coefficient (ADC) have been found to be helpful in assessing response as ADC values increase in responders [49, 50].

Ascitic tests

Typically, tubercular ascites is a low-serum ascites albumin gradient (SAAG) and high-protein ascites with a predominance of lymphocytes. However, this typical pattern may not be seen in patients with chronic liver disease (high SAAG), or malnutrition (low protein) [4]. Ascitic fluid cytology is routinely performed in patients with ascites and provides an opportunity to exclude important differential diagnoses, especially peritoneal carcinomatosis. Although typically lymphocyte dominance is seen in tubercular ascites, neutrophils could be predominant in early stages and peritoneal dialysis associated with TBP.

Ascitic adenosine deaminase

Adenosine deaminase (ADA) in peritoneal fluid offers a feasible, sensitive and highly specific test for TBP. While the multiple available test methods and different cut-offs by different studies can pose a challenge, as ascitic fluid tapping and analysis is easy to do and yields immediate results, ADA remains a relevant tool for screening and diagnosing PTB in India. Additionally, as PTB is a paucibacillary disease with low mycobacterial numbers, ADA has a special role given its sensitivity and specificity. Four meta-analyses have addressed the issue of diagnostic yield of ADA [9–12]. The most recent systematic review included 24 studies with 3,044 samples and found that the test had an excellent pooled sensitivity and specificity (93% and 95%, respectively) for the diagnosis of TBP. The PLR and NLR were also supportive of the use of this test. INDEX TB Guidelines suggest that a cut-off of 39 U/L be used for the diagnosis. However, there are certain caveats to the use of this test; false positives could occur in peritoneal carcinomatosis, lymphoma, hemorrhagic ascites and pus, while false negatives could occur in early stages or underlying cirrhosis (conflicting literature) [5, 51]. If the diagnosis of TBP is based solely on ascitic ADA, we usually perform paracentesis and cytological analyses three times to exclude peritoneal carcinomatosis with some degree of certainty [4, 5].

Microbiological tests on ascitic fluid

The yield of acid-fast bacilli (AFB) smear testing is extremely poor with a sensitivity of < 5%. We do not routinely perform AFB staining on ascitic fluid. Mycobacterial culture has a sensitivity of around 35%, but would be specific if positive [32]. There is a growing interest in PCR-based diagnostics, especially those which are available as point-of-care tools. Xpert Mtb/Rif has emerged as an important tool for microbiological diagnosis of pulmonary and some forms of extrapulmonary TB. The platform provides a point-of-care PCR-based diagnosis rapidly and safely. Additionally, it also provides information about rifampin resistance and helps in early diagnosis of multidrug-resistant tuberculosis (MDR-TB). Two systematic reviews have assessed the utility of Xpert Mtb/Rif testing for TBP [14, 15]. In one systematic review, 18 included studies and 1099 samples were included. The pooled sensitivity and specificity with respect to culture as a gold standard were 64% and 97%, respectively. However, against a comprehensive reference standard (eight studies, 643 samples), the pooled sensitivity and specificity

were 30% and 100%. There are reports of other PCR-based tests, but these tests have not been validated. In a study of multiplex PCR (16SrRNA, IS6110, and devR-based primers), the sensitivity was 75.7% with a specificity of 100%, but the validation of this approach is required [52].

Morphological or visual appearance

Laparoscopy

Laparoscopy with peritoneal biopsy is a tool for rapid and accurate diagnosis of TBP. However, it is not commonly performed due to the invasive nature of the procedure, complications such as bowel perforation and bleeding and lack of availability at peripheral setups. Classical patterns of TBP on laparoscopy were described as peritoneal thickening with yellow-white tubercles and the visual appearance was reported to be diagnostic in a majority of cases [53]. Peritoneoscopy also provides an opportunity to sample the lesions and achieve a histological or microbiological confirmation.

Colonoscopy findings

Because the ileocecal region and the ascending colon are the most frequent sites of involvement in GITB, ileocolonoscopy is an important tool in diagnosing GITB. The procedure provides an opportunity to evaluate the morphological pattern of involvement and also obtain tissue for histological and microbiological evaluation. Although none of the endoscopic findings are specific to GITB, some findings are considered to be suggestive of GITB. In a systematic review published in abstract form by Du et al., 12 studies with 1134 patients were included. While the presence of transverse ulcers (sensitivity: 43% and specificity: 88%) and a patulous ileocecal valve (sensitivity: 38% and specificity: 91%) was suggestive of GITB, the presence of aphthous ulcers, cobblestone appearance, skip lesions and longitudinal ulcers was more suggestive of CD [54]. In a Bayesian meta-analysis that studied multiple parameters, these findings were confirmed [55].

Intestinal biopsy-based tests

Microbiology

The diagnosis of ITB often relies on testing of the intestinal tissue. It is important to obtain adequate tissue samples for evaluation. A study suggested that taking eight pieces (instead of four) increased the positivity of Mycobacterium Growth Indicator Tube-960 (MGIT) culture from 40% to 52.8% [56]. In real life, it may sometimes be difficult to obtain adequate tissue because samples are needed for multiple tests (histopathology, culture, polymerase chain reaction/Xpert Mtb/Rif). A recent standard treatment workflow by Indian Council of Medical Research (ICMR) suggested that at least six biopsy pieces be obtained in sterile saline for microbiological testing [54].

Microbiological positivity is the gold standard for the diagnosis of GITB. The tissue obtained by surgery/colonoscopy should be subjected to microbiological testing. Although AFB staining is extremely important for pulmonary samples, the positivity rates are extremely low for GITB. TB culture provides an important tool for the diagnosis of GITB and also helps in testing for drug sensitivity in appropriate clinical settings. Culture positivity has been reported to vary from 7% to 79%, but is usually less than 50% [35]. MGIT may be preferable to the traditional culture in the Lowenstein-Jensen medium [57]. This is because MGIT provides early detection and possibly has higher sensitivity.

In a systematic review of nine studies with 709 patients, the sensitivity and specificity of IS6110-based PCR testing for the diagnosis of GITB were 47% and 95%, respectively [22]. In a systematic review of five studies with 460 samples, the pooled sensitivity and specificity of Xpert Mtb/Rif for the diagnosis of GITB using intestinal tissue were 23% and 100%, respectively, as compared to a composite reference standard [15]. No reports are available on the utility of newer PCR-based diagnostics such as Xpert Ultra. One study has reported that the sensitivity and specificity of Truenat MTB Plus (TruPlus) were 70% and 100%, respectively [58]. As with peritoneal tuberculosis, multiplex PCR based on multiple probes has been found to be sensitive and specific but needs validation [52, 58].

Histopathology

Histopathological evaluation plays an important role in the diagnosis of GITB and its discrimination from CD. The findings on histology may include the presence of epithelioid cell granulomas, caseating necrosis, confluent granulomas and changes of chronic inflammation [59]. Since GITB is usually a paucibacillary disease, clinicians may have to rely on histology for the diagnosis. In a systematic review of diagnostic accuracy, including 10 studies with 692 patients, three histological features were found to have high specificity for the diagnosis of GITB (as compared to CD). These included caseating granuloma (sensitivity of 0.21 and specificity of 100%), confluent granuloma (sensitivity of 0.38 and specificity of 99%) and ulcers lined by histiocytes (sensitivity of 0.41 and specificity of 94%) [23]. These three features, although specific, have poor sensitivity and none of these is positive in half of the cases of GITB. Therefore, a conclusive histopathological diagnosis is only possible in some cases. Further, granulomas in GITB are predominantly submucosal

in location and are dense (> 5/high-power field [HPF]) and relatively larger in size (macrogranuloma, > 200 µm) [55, 60]. The presence of lymph nodal granuloma in the absence of intestinal inflammation is highly specific for TB. Granulomas in CD are commonly smaller in size (microgranuloma, < 200 µm), discrete and fewer in number [60].

Table 3 provides the sensitivity of various modalities for the diagnosis of TBP and GITB.

Treatment and response

Antitubercular therapy and duration

A Cochrane meta-analysis of three RCTs (328 participants) compared the six-month regimen with the nine-month regimen of ATT to treat adults with abdominal TB. The relapse rates were not higher in patients who received a shorter duration (six months) of therapy with isoniazid, rifampin, pyrazinamide and ethambutol. Also, the clinical cure rates at the end of therapy were similar between the two groups [17]. Out of the three RCTs, only one included participants with PTB. The participants in this trial were treated thrice weekly under a directly observed therapy program and followed up for 12 months after completing ATT. No difference was reported between the six-month and nine-month regimen on per-protocol analysis (91.5% vs. 90.8%) or intent-to-treat analysis (75% vs. 75.85%) [59]. Additional observational data suggest that six months of therapy is sufficient in most cases, although the guidelines provide clinicians with an option of extending the duration of therapy on a case-to-case basis [28].

Role of steroids

Corticosteroids could potentially offer benefits when used as an adjunctive by reducing inflammation and preventing post-inflammatory fibrosis and are used in TB meningitis and pericardial TB. A meta-analysis evaluating the use of steroids for PTB showed adjunctive steroids used with ATT were more effective when compared with using ATT for the prevention of composite endpoint, symptomatic stricture and intestinal obstruction. However, the study noted that due to the poor quality of studies involved in the review and meta-analysis, the findings could not be generalized and there is a need for prospective well-controlled trials [16]. Therefore, routine use of steroids is not recommended for abdominal TB.

Endoscopic interventions and surgery

Stricturing disease is common in GITB and may occur in a quarter of patients with GITB. While three-fourths of the stricturing disease have a clinical response to ATT (unpublished meta-analysis), many patients continue to be symptomatic even after ATT and require additional therapy (endoscopic dilatation or surgery) [61, 62]. Further, many patients may present directly with intestinal obstruction and may need emergency surgery. In patients with ongoing symptoms in spite of ATT, endoscopic dilatation could be done for endoscopically reachable strictures [62]. The endpoint of dilatation is not well defined, but symptom resolution is aimed for. Usually, endoscopic dilatation is safe and efficacious [62]. Indirect evidence from CD-related strictures suggests a dilatation of 15–18 mm and passability of a standard colonoscope as additional criteria, but these have not been validated in the setting of GITB [35]. Strictures in GITB are likely to behave differently from CD-related strictures because effective ATT would ensure the absence of ongoing inflammation and therefore, the effects of dilatation may be more lasting. Apart from through-the-scope (TTS) balloon dilatation, for which data is available, there is no data for additional modalities, including endoscopic stricturotomy, in GITB. Certain patients may require surgery, especially if they are suffering from unrelenting intestinal obstruction,

Table 3 Sensitivity of various tests for diagnosis of gastrointestinal tuberculosis and peritoneal tuberculosis

Test	Gastrointestinal tuberculosis	Peritoneal tuberculosis
AFB stain	< 5%	3%
Xpert MTB/RIF	23% against a composite reference	30% against a composite reference 60% against culture
Adenosine deaminase	Not applicable	93% to 100%
MTB PCR (IS6110)	47%	25% to 80% (usually around 50%)
Multiplex PCR	75%	89%
Cultures	7% to 80% (usually around 40)	35%
Histology		NA
Confluent granuloma	38%	
Caseation	21%	
Ulcers lined by epithelioid histiocytes	41%	

AFB acid fast bacilli, *MTB PCR* Mycobacterium tuberculosis-polymerase chain reaction test, *NA* not applicable

recurrent abdominal pain or episodes of obstruction, massive gastrointestinal bleeding or perforation peritonitis [63, 64].

Response assessment

As mentioned earlier, the diagnosis of abdominal TB is difficult because of the low positivity of microbiological tests. Certain diseases may closely mimic abdominal TB—like peritoneal carcinomatosis (mimics TBP) and CD (mimics GITB). Unfortunately, clinical responses to ATT can be misleading. There is evidence to suggest that antimycobacterial therapy may result in clinical response in patients with CD [65, 66]. On the other hand, patients with GITB may continue to be symptomatic due to underlying strictures. In cases where the initial diagnosis was uncertain, it is important to look for objective evidence of response to ATT. Trial of ATT (variably termed as a diagnostic trial or a therapeutic trial) is the standard strategy to discriminate GITB and CD in TB-endemic areas. For ITB, healing of ulcers with ATT is an objective criterion of response to ATT, while the resolution of ascites is the criterion in PTB [66, 67]. Because the delay in diagnosis of CD due to ATT could potentially result in worse outcomes, it is important to make the discrimination between the two entities as early as possible. In a study of > 700 patients with CD, ATT was responsible for a diagnostic delay and could result in clinical response even in CD. A diagnostic delay was associated with more stenosing complications and the need for surgery [68]. In another report, the progression of an inflammatory pattern of CD to stricturing disease was reported with the administration of ATT [69].

In this regard, multiple studies have suggested that objective evidence of mucosal healing can be seen early (at two months) and could potentially reduce unduly prolonged ATT [70, 71]. Also, a two-month colonoscopy to look for early mucosal response provides an opportunity to identify and address the causes for lack of response, including alternative diagnosis or drug resistance [70]. In patients who are not willing to undergo colonoscopy, biomarkers such as fecal calprotectin can be used as a surrogate marker of mucosal response [72, 73]. Fecal calprotectin appears to be a better biomarker as compared to serum C-reactive protein (CRP) measurements [72]. The utility of these non-invasive parameters for follow-up was demonstrated in a study performed during the coronavirus disease - 19 (COVID-19) pandemic, when physical follow-ups were difficult and endoscopic procedures restricted [74].

Follow-up in other types of abdominal TB utilizes a combination of imaging and clinical follow-up [75]. Tubercular abdominal cocoon could respond clinically to ATT, but a significant number will require surgery [76].

Drug resistance

Drug resistance is an important global concern with regard to TB. Drug resistance in abdominal TB is likely to be similar to overall drug resistance in a particular region. Several studies have reported drug resistance in GITB. In a culture-based study from Western India, of the 43 patients with culture positivity, 23% had resistance to at least one first-line drug, while 14% had MDR-TB [77]. In a recent study on 30 ileocecal biopsies with positive TB cultures, four each (13.3%) had isoniazid and MDR, while two each (6.7%) were pre-extremely drug resistant (XDR) and mono-fluoroquinolone resistant [78]. This finding needs to be interpreted with caution, as only a subset of patients had positive cultures. Another study from the Western India reported an MDR-TB rate of 11.5% [79]. The rates were much lower (4%) in an Xpert Mtb/Rif-based study from Northern India [80].

Figure 2 summarizes an evidence-based approach to the evaluation and treatment of abdominal TB and is largely consistent with ICMR standard treatment workflow.

Additional types of abdominal tuberculosis

Gastroduodenal tuberculosis

The stomach is an uncommon site of TB but could present with symptoms such as epigastric pain, gastric outlet obstruction, hematemesis and failure to thrive (in children) along with constitutional symptoms. Endoscopic findings can include ulcers, mass or growth, nodularity, stricture or extrinsic compression [81]. Deeper biopsies using endoscopic mucosal resection or well technique (biopsy upon biopsy) may improve the diagnostic yield. Endoscopic ultrasound could help in targeting extraluminal lesions, including the lymph nodes. Gastric cancer is an important differential diagnosis. Endoscopic balloon dilatation (usually successful) or surgery may be needed if obstructive symptoms do not improve with ATT [81, 82].

Pancreatic tuberculosis

Pancreatic TB is another uncommon manifestation of TB that closely mimics pancreatic cancer. It usually presents as a solid pancreatic mass (especially in the head of the pancreas), but may present as a cystic lesion or peripancreatic lymphadenopathy [83]. The clinical manifestations may include abdominal pain, jaundice and constitutional symptoms. Although it was usually diagnosed as a histological surprise for surgical resection of presumed pancreatic

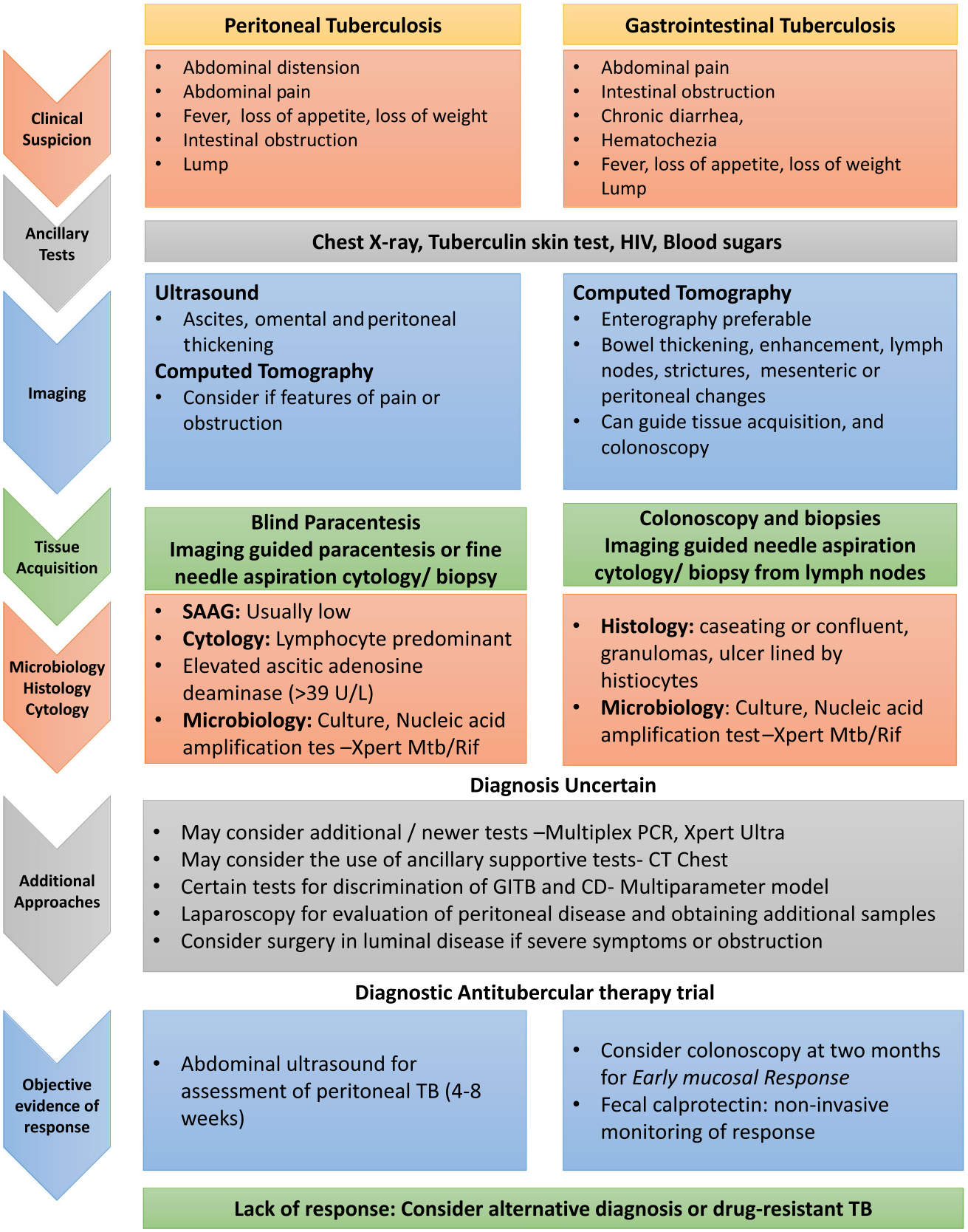

Fig. 2 Algorithmic approach to diagnosis and evaluation of abdominal tuberculosis. *HIV* human immunodeficiency virus, *ADA* adenosine deaminase, *CT* computed tomography, *PCR* polymerase chain reaction, *CD* Crohn's disease, *TB* tuberculosis

cancer, the advent of endoscopic ultrasound has resulted in more cases being diagnosed as part of the evaluation of pancreatic masses. It should always be considered in the differential diagnosis of pancreatic masses in TB-endemic regions [84].

Hepatobiliary tuberculosis

Hepatic involvement in TB could occur as part of localized disease (mass or tuberculoma or abscess) or systemic disease (granulomatous hepatitis). The clinical presentation could be due to systemic disease (fever, weight loss, organomegaly) or local disease (abdominal pain or tenderness) [85]. Liver biopsy has an excellent yield in granulomatous hepatitis, while image-guided fine-needle aspiration biopsy can help achieve diagnosis in localized forms of the disease. Microbiological yield from hepatic lesions is usually good [86]. Hepatic tuberculosis should be considered in non-resolving liver abscess, hepatic space-occupying lesion(s) or infiltrative pattern of liver function tests with predominant alkaline phosphatase elevations. Biliary involvement could also occur in the form of biliary strictures or lymph nodal compression of the biliary system [85]. Gallbladder TB is very rare and mimics gallbladder cancer [86, 87].

Future aspects

The low sensitivity of microbiological tests is the Achilles heel in the diagnosis of abdominal TB. It is unclear if increasing the amount of tissue or ascitic fluid could increase the mycobacterial yield on culture or other microbiological tests. It also remains to be seen if improvement in PCR-based diagnostics could improve the diagnostic yield. The use of newer diagnostic tests such as Xpert Ultra, although reported to have better sensitivity for the diagnosis of tuberculous pleural effusions, has not been reported for TBP [88]. Xpert XDR could also help in the detection of drug resistance to second-line therapies but has not been tested in abdominal TB. Multiplex PCRs which have shown to be of excellent sensitivity and specificity need to be validated in multicenter prospective studies before the clinical application can become routine.

The evaluation of small-bowel TB has been difficult because of the difficulty in accessing this region. Capsule endoscopy could help visualize the lesions but is limited by the inability to sample the lesions [89]. Advancements in small-bowel endoscopy including motorized spiral endoscopy could help improve the diagnosis of small-bowel TB. The other interest has been in using biomarkers including tumor markers (to discriminate TBP from peritoneal carcinomatosis), cytokines, CD4 + CD25 + FOXP3 + T-regulatory cells > 31.3% in peripheral blood (to discriminate GITB and CD), proteomic-based approaches, and nuclear medicine, including fluorodeoxyglucose (FDG)-positron emission tomography (PET) CT [90–94]. While some of these approaches have not been helpful, others, like the use of T-regulatory cells, appear promising but need validation at additional centers and assessment of feasibility before routine application. Some reports have evaluated the use of artificial intelligence, including its application on textual data (reports) or radiological images with fair discriminative power, but these are, as yet, beyond the realm of clinical use. Multiparameter models have also been assessed, and a model based on a Bayesian network meta-analysis seems to perform better than other models and is available online to discriminate ITB and CD [55].

Abdominal TB continues to be an important concern in many regions of the globe. The rising incidence of IBD in these regions poses additional challenges for diagnosis and management. Low diagnostic yield of microbiological tests in ascitic fluid and tissue biopsies is a concern and necessitates a diagnostic trial of ATT in a subset of patients. Close follow-up with objective evidence of response to ATT is essential in such cases.

Declarations

Conflict of interest DKJ, MMP, and VS declare no competing interests.

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