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Modern Tools for Diagnosis in Tuberculous Ascites

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Abstract

Tuberculosis (TB) is a highly contagious bacterial infection caused by *Mycobacterium tuberculosis* (MTB), affecting about 1/3rd of the world population and being responsible for lot of deaths worldwide, despite the progress achieved in the diagnosis and treatment fields. TB can affect the peritoneum, the TB ascites being a concern for physicians, especially when dealing with immunocompromised patients. The clinical presentation of TB ascites is challenging, due to nonspecific symptoms that make confusion with other diseases and the late results of cultures from ascites. The late diagnosis leads to a delayed treatment and high mortality. This manuscript describes recent tools used for early diagnosis in TB ascites. Molecular methods based on mycobacterial nucleic acid amplification tests (NAATs), polymerase chain reaction (PCR) detecting minimal amounts of bacterial DNA, or interferongamma release assays (IGRA) and biochemical methods such as the serum-ascites albumin gradient (SAAG) <1.1 g/dL, ratio between lactic dehydrogenase (LDH) in ascites fluid/serum total protein (TP) ratio of 0.5 and fluid ascites/serum LDH ratio of 0.6, and adenosine deaminase activity (ADA) > 40 UI/ml were recently considered more accurate diagnostic procedures. These methods allow a rapid and accurate differential diagnosis of ascites fluid, making possible the early treatment with appropriate drugs.

Keywords: peritoneal tuberculosis, ascites, diagnosis, molecular tests, biochemical tests

1. Introduction

Tuberculosis (TB) is a dangerous infection affecting about one third of the world population despite the availability of affordable and effective chemotherapy, remaining one of the major

causes of death from a single infectious agent worldwide. The most affected organ is the lung. It is preventable through Bacillus of Calmette and Guérin (BCG) vaccination and curable with antituberculous drugs.

Tuberculosis is a serious and highly contagious bacterial infection which in humans is usually caused by bacteria called *Mycobacterium tuberculosis* (MTB), a member of the *Mycobacteriaceae* family. This complex also includes *M. bovis* and *M. africanum*. *M. bovis* is more frequently found in cattle and other animals, but it's also responsible for some cases in humans. *M. africanum* is more common in West African countries. Mycobacterial infection is spread through the air from one person to another and causes active disease or latent infection [1].

The absolute number of incident cases has been decreasing since the early 2000s. The lowest incidence rate is found in high-income countries including the United States of America, Canada, New Zealand, Western Europe, and Australia. The largest number of incident cases is found in low- and middle-income countries. In 2015, 61% of the new cases occurred in Asia, followed by 26% new cases in Africa (Figure 1) [2].

The HIV infection is the prevalent risk factor for the development of TB because HIV alters the pathogenesis of TB by producing a progressive decline in cell-mediated immunity and raises the chances of extrapulmonary involvement [3, 4].

Tuberculosis is a disease which typically involves the respiratory system, being characterized by the growth of tubercles in tissues, but it can affect any other organ, in which case it's called extrapulmonary tuberculosis (EPTB) and usually results from hematogenous dissemination, being particularly present in immunocompromised patients. In some cases the infection directly extends from an adjacent organ. The most common sites of extrapulmonary tuberculosis are the lymph nodes, abdomen, bones and joints, pleura, spinal cord, and brain [5, 6].

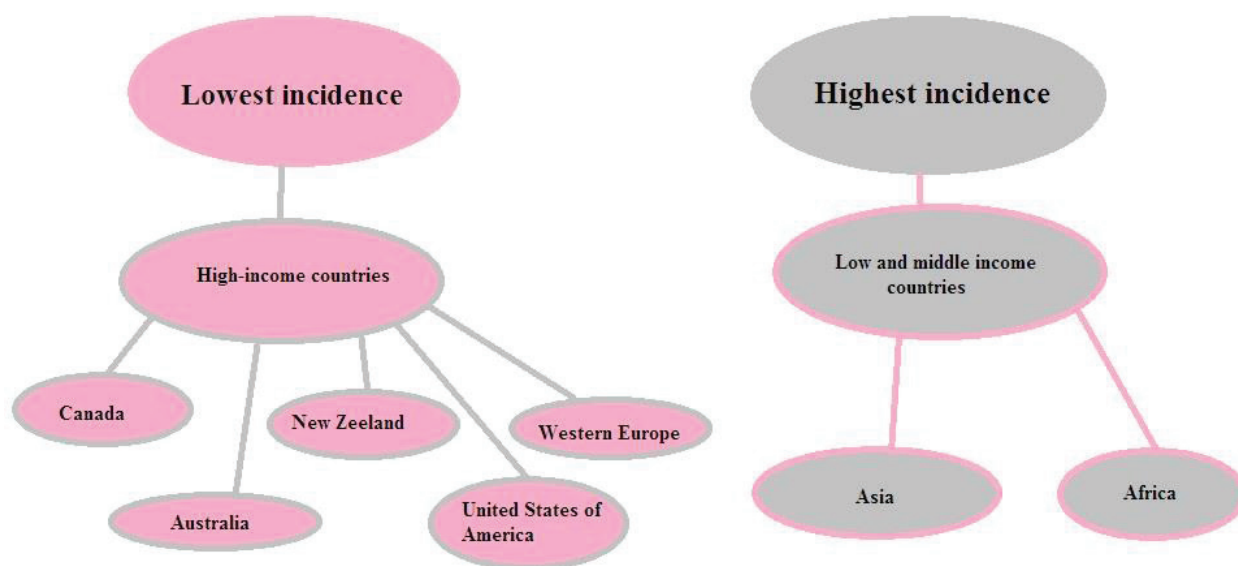


Figure 1. Worldwide incidence of TB infections.

Abdominal tuberculosis is a common form of extrapulmonary tuberculosis. The infection involving *M. tuberculosis* or *M. bovis* could be the result of a primary infection or the reactivation of a latent focus in immunocompromised patients. The spread of abdominal tuberculosis can be hematogenous or can result from direct contact with primary focus or ingestion of sputum containing bacilli from the active pulmonary focus. This form of EPTB affects the peritoneum, the gut, the abdominal lymph nodes, and sometimes, less frequently, the parenchymatous organs in the abdomen like the spleen, liver, and pancreas leading to severe complications. There are three types of abdominal tuberculosis: ascitic, obstructive, and glandular. Diagnosis can be achieved through different methods: ultrasound of the abdomen, CT/MRI scans, biopsies of the suspected organ, endoscopy, and various function tests.

Peritoneal tuberculosis is an uncommon site of extrapulmonary infection caused by *M. tuberculosis*. Patients susceptible of developing EPTB are those with malignant diseases, HIV infection, diabetes, and cirrhosis or patients treated with antitumor necrosis factor (TNF) agents or peritoneal dialysis. Peritoneal TB is divided into three types: the wet ascitic type, the fixed fibrotic type, and the dry plastic type. The wet ascitic type is more common and is associated with large amounts of free or loculated fluid in the abdomen. The high attenuation of the ascites in abdominal ultrasound is thought to be due to high protein and cellular content. Associated peritoneal enhancement is usually present.

Infection occurs frequently following reactivation of latent tuberculous in the peritoneum from hematogenous spread from a primary lung focus. It can also occur via hematogenous spread from active pulmonary or miliary TB. Not so often, the organisms enter the peritoneal cavity transmurally, from an infected small intestine or contiguously from tuberculous salpingitis. Over time, the visceral and parietal peritoneum becomes studded with tubercles [7–9].

2. Definition

Ascites is defined as an abnormal accumulation of fluid in the peritoneal cavity, the presence of serous fluid between the visceral and parietal peritoneum. The word ascites is derived from the ancient Greek word “*askos*” meaning a bag or a sack. Under normal circumstances, the amount of peritoneal fluid depends on a balance between plasma flowing into and out of the blood and lymphatic vessels. This balance, once being disrupted, leads to abnormal accumulation of fluid [10]. Ascites can be a consequence or a complication of infections, malignancy, and many severe diseases: cardiac, endocrine, hepatic, or renal. The prognosis is usually poor, but it depends on the underlying causes. Laboratory tests of ascitic fluid, clinical, paraclinical, and pathological data are required for the differential diagnosis.

Tuberculous ascites, one of the clinical signs of abdominal TB, implies accumulation of fluid in the abdomen, a swollen abdomen, and slightly raised tubercles of 1–2 mm all over the peritoneum. In EPTB, ascites develops secondary to “exudation” of proteinaceous fluid from the

tubercles, similar to the mechanism leading to ascites in patients with peritoneal carcinomatosis, and it's often misdiagnosed in elderly patients. Most patients with tuberculous peritonitis have ascites at the time of diagnosis, while the rest present the advanced phase, the dry or fibroadhesive form of the disease [11, 12].

3. Clinical manifestations

Tuberculous peritonitis is a subacute disease, and its symptoms evolve over a period of several weeks or months.

The insidious onset of this condition and the fact that the diagnosis is rarely suspected explains why patients have symptoms for more than 4 months before the diagnosis is established. Tuberculous peritonitis should be considered in any patient presenting with several weeks of abdominal pain, fever, and weight loss. Systemic and constitutional manifestations are common. Symptoms may be mild, with fatigue, abdominal pain, and tenderness, or severe enough to mimic acute abdomen [13]. Other clinical manifestations could be:

- Constipation/diarrhea
- Nocturnal hyperhidrosis
- Low-grade fever
- Anorexia
- Malaise

The clinical presentation of TB ascites is challenging, since it is nonspecific and can be confused with a plethora of other infectious or noninfectious diseases, leading to a delayed diagnosis and treatment which are major factors that contribute to the high mortality of TB.

Another situation that contributes to a delayed diagnosis is the presence of multiple comorbidities such as HIV/AIDS, cirrhosis, uremia, or other chronic conditions. Additional illness results in atypical presentation of TB ascites which render the symptoms more difficult to identify and distinguish. Moreover, in elderly patients, clinical manifestation is minimal with abdominal discomfort, constipation, or fatigue, symptoms that most people tend to ignore as minor or non-perilous (**Figure 2**) [14, 15].

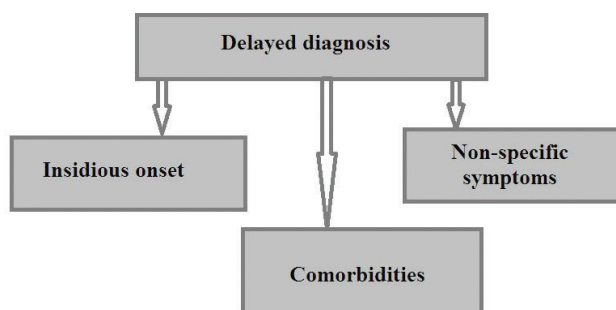


Figure 2. Factors associated with delayed diagnosis.

4. Diagnosis

Due to the fact that the nature of this disease is insidious, the diagnosis represents a challenge for clinicians. With the ever-increasing demographic shifts, more cases are now detected in areas where TB was a rarity until present. Unless a high degree of suspicion is maintained, the diagnosis can easily be missed or delayed [12].

Diagnostic techniques and procedures include:

- Clinical observation
- Imaging techniques: ultrasound, CT/MRI
- Laboratory tests
- Ascites fluid microbiologic and biochemical analysis

Generally, diagnosis is based on clinical suspicion, imaging of tuberculous infected zone, and detection of *M. tuberculosis* in ascitic fluid using acid-fast bacillus staining or culturing. The sensitivity of standard diagnostic methods such as Ziehl-Neelsen staining of smears and Lowenstein-Jensen culture done from ascitic fluid is very low for the diagnosis of abdominal TB. Ziehl-Neelsen staining of the ascitic fluid for mycobacterial detection is positive in only about 3% of the cases with proven TB peritonitis. Detection of mycobacteria requires the presence of more than 5000 bacilli/mL of specimen. In comparison, for positive culture, the presence of at least 10 organisms is considered to be sufficient. For a successful detection, culture methods based on a combination of liquid or biphasic media, together with solid media, are necessary [16, 17].

Nucleic acid amplification tests (NAATs) are molecular diagnostic methods based on amplification of mycobacterial nucleic acid. These are rapid methods that provide results within a day, and they are more specific and sensitive than Acid-Fast Bacillus Smear (AFB) smear. Albeit NAATs were originally designed for respiratory specimens, they can also be used on specimens from other TB sites like ascitic fluid samples, but this technique is still under evaluation.

Ascites of TB peritonitis obtained through ultrasound-guided paracentesis is an exudative type, and macroscopically its appearance is chylous and cloudy or turbid. Biochemically, the serum-ascites albumin gradient (SAAG) is now considered a more sensitive and specific measure than the ascitic total protein concentration which has been used for many years, in differentiating the ascites due to portal hypertension from ascites due to other pathophysiological mechanisms, such as tuberculous ascites which has a SAAG <1.1 g/dL and total proteins >3–4 g% [18, 19]. Combining LDH with total protein analysis has been explored for ascitic fluid. The cutoff values for three parameters in the ascitic fluid for differentiation between hepatic and non-hepatic ascites are as follows: LDH of 400 Sigma units, fluid/serum total protein (TP) ratio of 0.5, and fluid/serum LDH ratio of 0.6. The presence of any two of these three findings is usually associated with TB; the absence of all three indicates a hepatic cause [20].

Glucose concentration in the ascitic fluid, under normal conditions, is similar to that in the serum. Ascitic glucose concentration decreases due to consumption by bacteria, white blood cells, or cancer cells in the fluid in TB peritonitis. Ascitic glucose concentration is lower than

normal in TB ascites, which makes it an indicator in differentiating tuberculosis from other diseases, such as cirrhosis. The ascitic/blood glucose ratio is a useful test in differentiating TB peritonitis from other causes of ascites [18].

Ascitic fluid adenosine deaminase activity (ADA) is considered a more sensitive and specific method used for early diagnosis of TB ascites. Even if the full physiological role of ADA is not yet completely understood, it is known that ADA values are notably higher (>40 U/L) in patients with TB ascites [21–23].

Non-biochemical tests of ascitic fluid, including cell counts, bacterial culture, and polymerase chain reaction (PCR), have an important role in diagnosing the cause of ascites.

The total cell count in tuberculous ascites is 150–4000/ μL , and the cytologic examination shows over 70–80% lymphocytes and more than 250 leucocytes/ mm^3 (**Table 1**).

The sensitivity of direct microscopic smear detection of acid-fast bacilli in the ascitic fluid (0–6%) and ascitic fluid mycobacterial culture (20–35%) is low, and because of the delay in obtaining the results of mycobacterial cultures of ascitic fluid, the mortality is high, and the value of these tests in the differential diagnosis of ascites is limited.

Recently, a new approach to the fast diagnosis of bacterial infections emerged, including tuberculosis. The advanced molecular techniques provided a new method represented by PCR which can detect minimal amounts of bacterial DNA and improves the rates of bacterial identification from 4 to 6 weeks for microbiological cultures to 24 hours. In diagnosing TB effusions, PCR appears to be an ideal tool, with 94% sensitivity and 88% specificity, becoming a rapid and reliable method for identification of infectious ascites [24].

The tuberculin skin testing (TST or purified protein derivative (PPD) skin test) is controversial, despite the high specificity of this test which is between 95 and 99%. Skin testing is currently used only for detection of latent infection because of its low sensitivity and low positive predictive value. At the moment, there are no recommendations for using this test to diagnose active

Type	Exudative
Appearance	Chylous and cloudy/turbid
Total cell count	150–4000/ μL
Leucocytes	>250/ mm^3
Lymphocytes	>70–80%
Total proteins	>3–4 g%
ADA	>40 U/L
LDH	>400 SU
Glucose	<6 mg/dL
SAAG	<1.1 g/dL

Table 1. Characteristics of tuberculous ascites.

disease like tuberculous peritonitis. At best, tuberculin skin testing can only offer auxiliary information. Several studies have reported positivity rates ranging between 24 and 100% with no significant difference between high and low endemicity areas. Currently, the recommendations about the cut point for the induration differ depending on the risk scale. For patients at low risk, the cut point is at 15 mm; in cases of moderate risk, the cut point is 10 mm, and for those at high risk, the cut point is 5 mm. Generally, about 50% of the patients would have false-negative reactions to this test, suggesting the fact that it has many potential sources of error. In conclusion, energy testing may yield confusing information and is no longer recommended for diagnosis [25].

A great scientific advance has been the development of an IFN- γ -based test with an 89% sensitivity, which is a quantitative *in vitro* assay evaluating the cell-mediated immune response to *M. tuberculosis* and has excellent agreement with tuberculin skin testing. The principle of this test is that previously sensitized T lymphocytes release IFN- γ in response to stimulation by purified protein derivative (PPD).

In the past few years, the tuberculin skin test has been replaced by T-cell-based interferon-gamma release assay (IGRA) which is more sensitive and more specific. IGRA is an *in vitro* test used in all circumstances in which the TST is currently used, including evaluation of immigrants, surveillance programs, or contact investigations [26]. There are three commercially available IFN- γ tests: QuantiFERON-TB Gold assay (QFN-Gold), QuantiFERON-TB Gold *In-Tube* assay (QFN-G-IT), and T-SPOT.TB assay. They are rapid immunodiagnostic tests that can detect interferon- γ (IFN- γ) produced by lymphocytes in response to *Mycobacterium tuberculosis* (MTB). T-SPOT.TB test is a blood IFN- γ assay that measures the number of IFN- γ -producing T cells by identifying IFN- γ release when stimulated by MTB-specific antigens, including early secretory antigenic target 6 and culture filtrate protein 10, using enzyme-linked immunospot assay. QuantiFERON-TB Gold test is the predecessor of QuantiFERON-TB Gold *In-Tube* test, and they both measure production of IFN- γ in culture supernatant using enzyme-linked immunosorbent assay (ELISA). This measurement is possible by circulating T cells in whole blood being challenged with *M. tuberculosis*-specific antigens. The advantage of blood IGRA tests over tuberculin skin tests is the fact that IGRAs do not cross-react with the Bacillus of Calmette and Guérin (BCG) vaccine antigens, but suboptimal results can be possible in diagnosing EPTB because they aren't able to distinguish latent infection from active disease [27]. According to some researches, *M. tuberculosis* antigen-specific T cells may accumulate at infection sites; therefore, investigating body fluid IGRAs may increase the accuracy of EPTB diagnosis [28, 29].

Imaging techniques used for detection of TB ascites are ultrasound and computed tomography. These methods also increase the accuracy of several procedures like paracentesis or peritoneal biopsies, providing a safer and affordable replacement to diagnostic laparoscopy [30].

Ultrasound is the most sensitive and reliable method of detecting ascites, guiding paracentesis and monitoring the effects of therapy. It can detect even small volumes of fluid (as little as 100 ml of fluid could be detected). Ascites is usually seen as an anechoic space. In TB ascites, particulate matter within the ascitic fluid or fine, mobile strands, representing echogenic debris, can be detected. Less commonly, the ultrasound can reveal calcifications in the walls of encysted ascitic fluid [12].

On computed tomography the ascitic fluid has high attenuation values, between 20 and 45 HU, and the peritoneum is symmetrically thickened and nodular. Frequently, an early sign of abdominal TB is a thickened mesentery (>15 mm) with mesenteric lymph nodes.

Many studies concluded that ultrasonography and computed tomography are complementary to each other in detecting TB ascites, as they provide different details. CT focuses on the peritoneum and omental and mesentery involvement, and the ultrasound shows fine, mobile septations (**Figure 3**) [31].

However, the only certain way to diagnose TB ascites is the histological examination. Various methods that include excision, laparoscopy, needle biopsy and ultrasound-guided biopsies, endoscopy, computed tomography (CT), or endoscopic ultrasound are used to establish the

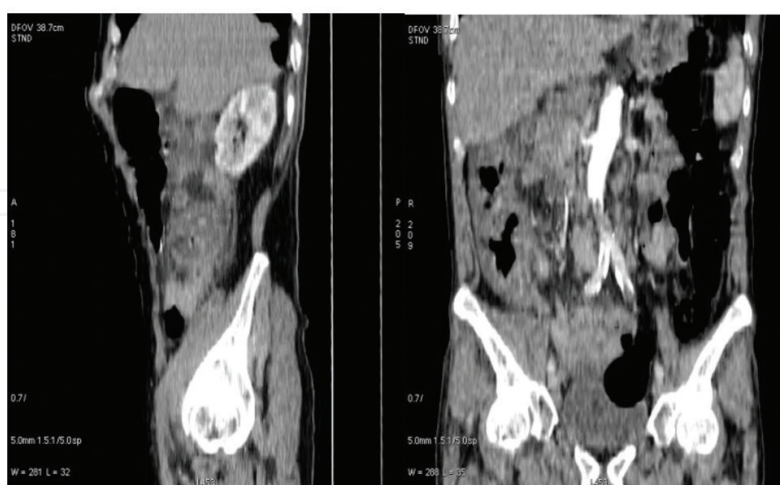
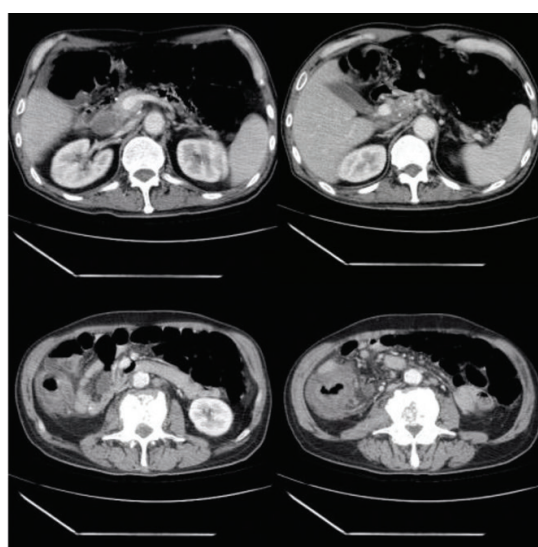


Figure 3. Circumferential parietal thickness, with an edematous appearance of the appendix, cecum, ascending colon, and up to the hepatic flexura, associating stripe thickening of adjacent fat. Multiple adenopathies containing calcifications and central necrosis. Fluid accumulation in the peritoneal cavity associating symmetrical, iodophilic thickening of parietal peritoneum. Osteolytic areas with an adjacent osteosclerotic reaction in L2, L3, and L4 vertebrae. Parafluid accumulation in L2–L3 and L3–L4 intervertebral spaces that reaches the anterior epidural space and the roots of L2 and L3 nerves, extending to L3–L4 adjacent smooth tissues, with no visible border toward the right psoas muscle.

diagnosis. The presence of granulomas is typical for TB ascites [32]. The relative sensitivities of different procedures and the potential therapeutic benefits should be considered in making the choice of diagnostic approach. In superficial TB lymphadenitis, fine needle aspiration (FNA) biopsy of affected lymph nodes is the gold-standard diagnostic technique. Excision biopsy has the highest sensitivity, whereas FNA is less invasive and may be useful. If FNA examination results are doubtful, excision biopsy may be needed. Laparoscopy with target peritoneal biopsy is the current first-line investigation in the diagnosis of peritoneal TB [33, 34]. Several studies revealed a diagnostic accuracy of 84–96% for TB peritonitis.

Generally, tissue biopsy is superior to fluid aspiration in providing positive culture results. The diagnosis is more accurate when the biopsy results and polymerase chain reaction assays are combined with culture results [35].

5. Differential diagnosis

The main differential diagnosis is peritoneal carcinomatosis, which can be difficult to distinguish, especially in older patients. The nodules of carcinomatosis are larger, usually more than 3 mm, more vascular, and more irregular than the tuberculous ones which rarely surpass 1–2 mm. Carcinomatosis is seen as an irregular peritoneal thickening with nodular implants, while TB peritonitis is suggested by the presence of a smooth peritoneum with symmetrical thickening, ascites, and enlarged lymph nodes of low attenuation [31].

Other less likely considerations include:

- Ascites in liver diseases: the liver is enlarged and irregular; proteins are lower than 4 g%.
- Nephrotic syndrome: ascites is less marked; proteins are lower than 4 g%.
- Nutritional edema (hypoproteinemia) has many other signs of protein deficiency; proteins are also lower than 4 g%.
- Starch peritonitis, sarcoidosis, and Crohn’s disease may resemble the laparoscopic features of TB peritonitis, but the presence of caseating granuloma establishes the diagnosis (**Table 2**) [36, 37].

The most important differential diagnosis	Less likely considerations
Peritoneal carcinomatosis	Ascites in liver disease
	Nephrotic syndrome
	Hypoproteinemia
	Sarcoidosis
	Starch peritonitis
	Crohn’s disease

Table 2. Differential diagnosis.

There are a few signs that additionally suggest the diagnosis of TB peritonitis: normal serum levels of CA 19–9 and carcinoembryonic antigen (CEA), elevated serum levels of CA 125, fever, and lymphocyte-predominant benign ascites, but only biopsies yield the final diagnosis [38, 39].

6. Treatment

Treatment is initiated not only in patients with confirmed diagnosis but also in patients with strong suspicion of TB, because a delay in treatment initiation can lead to significant mortality. TB treatment initiation includes also individuals with ascites associated with fever, weight loss, imaging signs of TB, personal history of TB, or contact with a tuberculosis case.

Despite the fact that most guidelines on the treatment of tuberculosis suggest that 6 months of treatment is sufficient for extrapulmonary tuberculosis (except for the case of bone tuberculosis or tuberculous meningitis), most physicians treating peritoneal tuberculosis use anti-tuberculous therapy for 9 to 12 months [40, 41].

Drug treatment is the most important modality and follows standard regimens and principles. There are currently five drugs that are considered first-line medications: isoniazid, rifampicin, pyrazinamide, streptomycin, and ethambutol. Second-line drugs are only used in case of resistance to first-line therapy (extensively drug-resistant tuberculosis or multidrug-resistant tuberculosis), and they are represented by aminoglycosides, fluoroquinolones, polypeptides, cycloserine, thioamides, and terizidone. There is also a third-line therapy with uncertain or unproven efficacy including rifabutin, macrolides, linezolid, thioacetazone, thioridazine, arginine, bedaquiline, and vitamin D [42]. Drug-resistant disease varies substantially in different areas of the world and may occur in cases of poor patient management, nonadherence to prescribed regimen, or as a result of malabsorption of the antituberculous drugs.

The treatment of TB peritonitis in patients with HIV is usually the same, but because HIV-infected patients are often taking multiple drugs, some of which may interact with antituberculous ones; it is strongly recommended to consult the experts in HIV-related TB.

The “complete response” to antituberculous treatment means complete resolution of symptoms and ascites within 6 months; in most cases, laboratory tests return to normal values within 3 months. Persistence of ascites means “no response” [43, 44].

7. Conclusions

Peritoneal tuberculosis is still common in areas of the world where TB is prevalent and its incidence ratio is likely to increase as a consequence of population migrations.

Ascites can be a complication of an aggregate of diseases, which carries an unfavorable prognosis that depends on the causes, the moment of diagnosis, and the start of the treatment.

Establishing the diagnosis of TB ascites requires a high index of suspicion because of its insidious development. In any patient with several weeks of abdominal pain, weight loss, fever, and lymphocytic dominant ascites with SAAG < 1.1 g/L, as well as in patients with ascites belonging to special population groups, such as indigenous or older people, or patients with ascites as the primary symptom, ascitic TB peritonitis should be considered in differential diagnosis. This syndrome behaves clinically like many abdominal diseases that are often ignored, leading to a significant impact on morbidity and mortality due to a delayed diagnosis and treatment. Older laboratory tests lack sensitivity and specificity in establishing the diagnosis. Histological examination, considered the gold-standard diagnosis method, is an invasive procedure with high risk of complications. More accurate methods such as molecular tests based on mycobacterial nucleic acid amplification tests (NAATs), PCR techniques used to detect bacterial DNA, or interferon-gamma release assays (IGRA) and biochemical methods such as the serum-ascites albumin gradient (SAAG), ratio between LDH in ascites fluid/serum total protein (TP) ratio and fluid ascites/serum LDH ratio, adenosine deaminase activity (ADA), and imagistic techniques were recently considered for an efficient positive diagnosis of TB ascites, making possible the early treatment with appropriate tuberculostatic drugs.

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