



Diverse clinical manifestations and management approaches in abdominal tuberculosis: A case series

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Abstract

Introduction: Abdominal Tuberculosis (TB) is a significant form of extra-pulmonary tuberculosis (EPTB), impacting the gastrointestinal tract, peritoneum, lymph nodes, and occasionally solid organs. While TB primarily affects the lungs, approximately 15% of cases are extra-pulmonary, with abdominal TB being one of the most frequent forms. Diagnosing abdominal TB is challenging due to its non-specific symptoms and low bacterial load, often leading to inconclusive microbiological tests and misdiagnosis with conditions like Crohn's disease or abdominal malignancies.

Epidemiology: The incidence of abdominal TB ranges from 2.7% to 21% of all EPTB cases, with a notable burden in India, where TB accounts for significant morbidity and mortality. Abdominal TB's association with other comorbidities, such as chronic liver disease, further complicates diagnosis and management, particularly in younger, female, and immunocompromised patients.

Clinical Presentation: Symptoms of abdominal TB are varied and often non-specific, including abdominal pain, fever, weight loss, and ascites. Diagnostic delays are common due to the subtlety of these symptoms, making early clinical suspicion critical. Imaging modalities like ultrasound and CT scans, along with microbiological and histopathological evaluations, are essential for accurate diagnosis.

Case Series

Case 1: A 47-year-old female with a history of pulmonary TB presented with abdominal distension. Imaging and FNAC revealed ascites and thickened ileo-cecal junction, consistent with TB. GenXpert confirmed the presence of Mycobacterium tuberculosis without rifampicin resistance. Due to suboptimal drug levels indicated by therapeutic drug monitoring (TDM), her regimen was adjusted, leading to successful treatment completion.

Case 2: A 24-year-old female presented with abdominal pain and vomiting, and imaging revealed lymphadenopathy with granulomas at the ileo-cecal junction. GenXpert confirmed TB without rifampicin resistance. The patient developed drug-induced hepatotoxicity, necessitating a temporary switch to hepato-safe drugs. Once stabilized, she resumed standard ATT and completed a 7-month course with clinical improvement.

Diagnostic Challenges and Management: Diagnosing abdominal TB requires a multidisciplinary approach, utilizing imaging, microbiological tests, and histopathological evaluations. Therapeutic drug monitoring (TDM) and close monitoring of drug-induced side effects, particularly hepatotoxicity, are crucial in managing complex cases. Individualized treatment regimens, including adjustments based on TDM and patient response, are essential for optimal outcomes.

Conclusion and Recommendations: Abdominal TB is a diagnostic challenge that requires a high index of suspicion, particularly in endemic areas. Comprehensive diagnostic and management strategies, including the use of advanced imaging, microbiological testing, and personalized treatment plans, are essential for improving patient outcomes. Regular follow-up and monitoring are necessary to ensure treatment success and prevent complications.

Keywords: Tuberculosis, extra-pulmonary tuberculosis EPTB, abdominal tuberculosis

Introduction

Tuberculosis (TB) is a serious and life-threatening infectious disease that poses a global health challenge. The World Health Organization has recognized it as a worldwide emergency ^[1].

Infection with Mycobacterium tuberculosis persists for life, and the bacterium affects nearly a quarter of the global population, leaving them at risk of progressing to active tuberculosis ^[2,3].

Tuberculosis impacts close to 10 million individuals and results in over a million deaths each year, even though it is a preventable and treatable disease ^[3].

Tuberculosis primarily affects the lungs, but about 15% of cases worldwide are extrapulmonary. Abdominal tuberculosis is one of the more frequent sites of extrapulmonary infection, typically involving the

gastrointestinal tract, peritoneum, lymph nodes, and solid organs, in that order. Diagnosing and treating abdominal TB can be difficult, as the disease often has a low bacterial count, leading to poor results in microbiological tests. Additionally, it closely resembles many other conditions, which can cause diagnostic uncertainty ^[4,5].

In some instances, less specific indicators like ascitic fluid adenosine deaminase levels are used for diagnostic purposes ^[6].

When the diagnosis is uncertain despite using various methods, a therapeutic trial with antitubercular treatment (ATT) is often initiated in regions where TB is common, and the response to the therapy is monitored. Due to the disease being predominantly an issue in developing countries, the progress in establishing evidence-based diagnosis and treatment has been slow. A recent survey of

doctors revealed considerable differences in clinical practices concerning diagnostic techniques, treatment duration, and follow-up procedures in abdominal TB [7].

A significant portion of the global TB burden, around 56%, is concentrated in the South East Asia and Western Pacific regions, with India alone accounting for a quarter of the cases. Abdominal TB represents about 12% of all extrapulmonary TB cases, making it one of the most prevalent forms of extrapulmonary TB. There has been an observed increase in cases in both developing and developed countries [4, 5].

In India, TB is responsible for approximately 550,000 deaths each year. Abdominal TB is particularly challenging to diagnose as it often lacks specific clinical symptoms, and current diagnostic tests have limited sensitivity. Additionally, it can be easily mistaken for other conditions such as Crohn's disease, abdominal cancers, or colitis, leading to significant diagnostic challenges. Therefore, early diagnosis through clinical suspicion is crucial for improving patient outcomes [6, 7, 8].

Epidemiology

The incidence of abdominal tuberculosis (TB) as a percentage of all extrapulmonary TB (EPTB) cases has been reported to range from 2.7% to 21% [25, 26] [9, 10]. In a study conducted across three states in India under the national tuberculosis program, abdominal TB accounted for 12.8% of all EPTB cases [26]. (10) Abdominal TB has been associated with lower treatment completion rates and poorer outcomes [10, 11]. Within abdominal TB, gastrointestinal tuberculosis (GITB) and tuberculous peritonitis are frequently observed [12, 13]. Due to potential selection bias, with pulmonary TB (PTB) being easier to diagnose through abdominal paracentesis, GITB is often cited as the most common form of abdominal TB in reports from tertiary care centers [9]. Certain comorbidities, particularly chronic liver disease, significantly increase the risk of developing abdominal/PTB [14]. Other risk factors for abdominal TB include younger age, female gender, Asian ethnicity, HIV coinfection, immunosuppression, diabetes mellitus, and peritoneal dialysis [14, 15, 16].

Pathophysiology [17]

Esophageal TB: This rare condition usually results from the spread of TB from adjacent tissues, typically affecting the middle third of the esophagus. It often presents with dysphagia and odynophagia.

Gastric and Gastroduodenal TB: Although proximal GITB was once considered rare due to protective factors like high acidity, it has been reported in the stomach and duodenum. It may occur secondary to pulmonary TB and can lead to complications like gastric outlet obstruction.

Small and Large Intestinal TB: This form of TB can present in four ways:

1. Ulcerative— Superficial transverse ulcers, more common in the small intestine.
2. Hypertrophic – Inflammatory masses, typically in the cecum.
3. Ulcero-hypertrophic – A combination of ulcerative and hypertrophic forms.
4. Fibrous stricturing – Can cause fibrosis and obstruction.

Rectal and Anal TB: Involvement here may mimic Crohn's disease or present as non-healing lesions, fistulae, or a circumferential mass.

Solid Organ TB: Involves organs like the gall bladder and liver through hematogenous spread, commonly seen in immunocompromised patients, particularly those with AIDS.

Peritoneal TB: Usually associated with other abdominal TB forms, it occurs after necrotic lymph nodes rupture, leading to ascites. TB peritonitis can present in ascitic, loculated, plastic, purulent, or nodular forms.

Clinical Presentation [16, 17, 18, 19, 20, 21, 22, 23]

A systematic review on tuberculous peritonitis revealed that the most commonly reported symptoms include abdominal pain (65%), fever (59%), weight loss (61%), diarrhea (21%), and constipation (11%). Ascites (73%), abdominal tenderness (48%), hepatomegaly (28%), and splenomegaly (14%) were the predominant clinical signs. General symptoms appear in about half of the patients, and due to the non-specific nature of these symptoms, diagnosis can be delayed by 7 to 24 weeks from their onset. Tuberculous peritonitis, though less common than gastrointestinal tuberculosis (GITB), can also present with signs of intestinal obstruction, particularly in cases with adhesions, peritoneal fibrosis, or sclerosing encapsulating peritonitis (abdominal cocoon).

Intestinal tuberculosis typically presents with abdominal pain (30% to 88%), fever (21% to 73%), diarrhea (5% to 47%), loss of appetite (30% to 90%), weight loss (8% to 80%), constipation (7% to 24%), and hematochezia (5% to 15%). Some patients may also experience intestinal obstruction (3% to 36%). Up to 25% of cases may have concurrent or prior pulmonary tuberculosis. The increasing prevalence of inflammatory bowel disease (IBD) in India has not significantly reduced the incidence of GITB, making differentiation between the two conditions an ongoing challenge.

The definitions and classifications for abdominal tuberculosis (TB) [24, 25, 26]

The definitions and classifications for abdominal tuberculosis (TB) vary widely, based on clinical symptoms, morphological patterns, diagnostic methods, and response to anti-tuberculosis treatment (ATT). Abdominal TB can be classified based on symptoms: intestinal TB presents with pain (strictures or hypertrophic lesions) or diarrhea (diffuse ulcers), while tuberculous peritonitis is either pain-dominant (due to peritoneal adhesions or fibrosis) or distension-dominant (ascites in peritoneal TB). However, the morphological classifications often overlap. A review suggested avoiding the classification of peritoneal TB into wet, dry, and fibrotic forms due to overlapping features. Therefore, a case definition that reflects the confidence level in diagnosis, aligned with INDEX-TB guidelines, is recommended. Microbiologically confirmed cases offer the highest diagnostic confidence, while clinically diagnosed cases vary in certainty. Findings like caseating granulomas or high ascitic adenosine deaminase levels add confidence, while a diagnosis based on clinical and radiological findings alone is less certain. The confidence level in diagnosis influences clinical management, requiring closer monitoring for those with less certain diagnoses.

Evaluation ^[17]

General Laboratory Testing: Patients with gastrointestinal tuberculosis typically exhibit lower hemoglobin, lower serum albumin, and elevated C-reactive protein (CRP) levels. CRP, erythrocyte sedimentation rate (ESR), and fecal calprotectin can be useful markers for monitoring treatment response in antituberculosis therapy (ATT).

Mycobacterium-specific Testing: Gastrointestinal tuberculosis is a paucibacillary disease, meaning acid-fast bacilli (AFB) may not always be detectable. Common tests, including acid-fast stains, cultures, and nucleic acid amplification tests, often show poor sensitivity. The Quantiferon test may yield false negatives in extrapulmonary TB cases, but interferon-gamma release assays have better sensitivity and specificity than tuberculin skin tests for diagnosing GI TB. However, they cannot differentiate between active and latent infections. The TBAg/PHA ratio might improve specificity for active TB. Adenosine deaminase (ADA) in ascitic fluid is a good diagnostic marker. Polymerase chain reaction (PCR) tests, while useful for initial diagnosis, are not suitable for follow-up since they cannot distinguish between living and dead bacteria. Multiplex PCRs and newer molecular techniques, including real-time assays, have improved diagnostic accuracy and can differentiate TB from Crohn's disease. Molecular probes detect drug resistance mutations with high sensitivity and specificity. WHO recommends a rapid PCR-based test that detects *M. tuberculosis* and rifampicin resistance within 2 hours, though it may have limited sensitivity for extrapulmonary TB.

Imaging ^[27]

CT scans are preferred for assessing GI TB, showing asymmetric wall thickening and necrotic lymph nodes, among other features. Ascitic fluid in TB has high protein content, and peritoneal TB manifests in different forms, including fibrous and nodular types. CT enterography is a newer technique for diagnosing and monitoring TB lesions. Ultrasound and ultrasound-guided aspiration, especially with laparoscopy, are useful for diagnosing peritoneal TB and solid-organ involvement.

Gastroenterology Procedures: Colonoscopy, often done for other reasons, can detect asymptomatic GI TB. Biopsies obtained during colonoscopy have up to 80% diagnostic accuracy, especially when multiple tissue samples are cultured.

Therapeutic Trials: In cases where diagnostic tests are inconclusive but clinical suspicion is high, empirical antituberculosis therapy (ATT) may be initiated, with the response to treatment considered as a diagnostic criterion. Response typically occurs within two weeks, though accuracy rates of therapeutic trials vary.

Treatment and Management of Abdominal Tuberculosis ^[28, 29, 30]

Medical Therapy: A standard four-drug regimen—isoniazid, rifampicin, pyrazinamide, and ethambutol—is recommended for the treatment of intra-abdominal/gastrointestinal tuberculosis. These drugs are administered thrice weekly for the first two months, followed by isoniazid and rifampin for an additional four

months. A 6-month course of therapy is typically effective, leading to good cure rates and early healing of intestinal ulcers. However, in cases of disseminated disease, prolonged therapy may be necessary. Each patient should be evaluated individually, and consultation with an infectious disease expert is advised.

Endoscopic Intervention: Endoscopic balloon dilatation can be used for managing ileal and duodenal strictures.

Surgical Therapy: Surgery may be required in cases of complications such as obstruction, perforation, or fistulation. Surgical options include:

Complications of gastrointestinal tuberculosis

Include upper and lower GI bleeding, fistulas, obstruction, strictures, intussusception, perforation, anemia, malnutrition, and vitamin/mineral deficiencies. It can be mistaken for Crohn's disease, with immune-suppressive therapy worsening outcomes. Rarely, intestinal TB may develop during Crohn's treatment. MDR TB is a concern, with some studies reporting a 13% prevalence in GI TB patients, often with concurrent pulmonary TB. Chronic inflammatory demyelinating polyneuropathy has been reported in one case.

Retrospective Observational Case Series**Case Series**

47yrs female having history of Pulmonary TB for 4months and on Anti TB treatment Rifampicin pyrazinamide ethambutol and Isoniazid, pyrazinamide was stopped after two months and rest medicine continued. One month back her abdomen started bulging, patient consulted her physician and Ultrasonography of abdomen was done, it shows free fluid in abdomen with thickened ileo caecal junction and multiple lymph nodes with granuloma, mostly tuberculosis, fine needle aspiration cytology FNAC done under USG guidance, specimen GenXpert shows *Mycobacterium tuberculosis* detected with no Rifampicin resistance, Ascites fluid removed which shows lymphocytes preponderance and ADA increased no malignant cells are seen. She was advised to do TDM this test tell us serum levels of Anti TB drugs and which was less than reference level. Patient was started on higher doses of anti -TB drugs. Patient started responding to Rifampicin pyrazinamide ethambutol and Isoniazid and completed the treatment

24yrs female patient history of Pain in Abdomen since two months, she has taken treatment for one month with General Practitioners and he advised USG Abdomen, it shows multiple lymph nodes with granuloma and caseation in ileo caecal junction and multiple enlarge mesenteric lymph nodes. Patient FNAC done under USG guidance and specimen send for GenXpert, which shows *Mycobacterium tuberculosis* detected with no Rifampicin resistance. Started on first line drugs Rifampicin pyrazinamide ethambutol and Isoniazid, initially weight increased and pain in abdomen started subsiding, after two weeks patient comes with history of Nausea and Vomiting, patient had not taken any food for two days, her weight also decreased. Liver function test shows increased in liver enzymes SGPT and SGOT. Patient Anti TB treatment stopped and hepatosafe drugs started like Levofloxacin, Ethambutol and Streptomycin. After two weeks LFT returns to normal and anti -TB drugs again started one by one. Patient continue with

treatment and was clinically significant improvements with increasing weight. Patient was given Anti TB treatment for 7 months and stopped and declared treatment completed as patient is a case of Extra pulmonary TB.

Aim

To explore the diverse clinical presentations, diagnostic challenges, and management strategies of Abdominal Tuberculosis (TB) through a detailed analysis of a case series, highlighting the importance of comprehensive evaluation and multidisciplinary treatment approaches.

Objectives

- 1. To Describe Clinical Presentations:** Document and analyze the varying symptoms and clinical manifestations in patients diagnosed with Abdominal TB.
- 2. To Evaluate Diagnostic Approaches:** Review the diagnostic tools and methods used, including imaging, laboratory tests, and histopathological examinations, to confirm Abdominal TB.
- 3. To Analyze Differential Diagnoses:** Discuss the differential diagnosis process, distinguishing Abdominal TB from other gastrointestinal disorders such as Crohn's disease, malignancies, and other infections.
- 4. To Review Management Strategies:** Assess the treatment protocols, including medical therapy with anti-tuberculosis drugs and potential surgical interventions, along with monitoring and follow-up strategies.
- 5. To Highlight Outcomes and Challenges:** Present the outcomes of the cases, including response to treatment and long-term follow-up, while identifying challenges encountered in diagnosis and management.
- 6. To Provide Recommendations:** Offer recommendations based on the case findings for improving diagnosis, treatment, and overall management of Abdominal TB, particularly in settings where TB is endemic.

Discussion on Abdominal Tuberculosis Case Series

- 1. Overview of Abdominal Tuberculosis:** Abdominal tuberculosis (TB) is a form of extrapulmonary TB that can affect the gastrointestinal tract, peritoneum, lymph nodes, or solid organs. It is more prevalent in regions with high TB incidence and often presents with non-specific symptoms, making diagnosis challenging. The two cases presented in the series highlight typical presentations, diagnostic challenges, and treatment approaches.
- 2. Case Summaries: - Case 1:** A 47-year-old female with a history of pulmonary TB developed abdominal symptoms, including abdominal distension. Ultrasonography revealed ascites, thickened ileo-cecal junction, and lymphadenopathy suggestive of TB. FNAC confirmed TB without rifampicin resistance, and therapeutic drug monitoring (TDM) indicated

suboptimal levels of anti-TB drugs. The patient was treated with an intensified regimen and showed a good response, completing the treatment successfully.

Case 2: A 24-year-old female presented with abdominal pain and was found to have lymphadenopathy with granulomas in the ileo-cecal junction. GenXpert confirmed TB without rifampicin resistance. Initially treated with standard anti-TB therapy, she developed drug-induced hepatotoxicity, necessitating a change to hepatic safe drugs. After stabilization, she resumed standard treatment and completed a 7-month course, showing clinical improvement.

- 3. Diagnostic Challenges and Tools:** Both cases underscore the challenges in diagnosing abdominal TB due to its non-specific symptoms and the need for detailed imaging and microbiological investigations. Ultrasonography, FNAC, and GenXpert testing were crucial in establishing the diagnosis. The presence of granulomas and detection of *Mycobacterium tuberculosis* with no rifampicin resistance were key findings.
- 4. Treatment and Management:** The standard anti-TB regimen, including rifampicin, isoniazid, pyrazinamide, and ethambutol, was used in both cases. However, individualized treatment adjustments were necessary. In Case 1, subtherapeutic drug levels required dose adjustment, while in Case 2, drug-induced hepatotoxicity necessitated temporary cessation and substitution with hepatosafe drugs (levofloxacin, ethambutol, and streptomycin). Monitoring liver function tests (LFTs) was critical in managing drug-induced liver injury.
- 5. Importance of Therapeutic Drug Monitoring (TDM):** TDM played a crucial role in Case 1, revealing suboptimal drug levels that were corrected by adjusting dosages. This highlights the importance of TDM in managing TB, especially in cases with complicated pharmacokinetics or potential drug interactions.
- 6. Outcome and Follow-up:** Both patients completed their respective treatment courses and showed clinical improvement, including weight gain and resolution of symptoms. The duration of treatment in Case 2 (7 months) was slightly shorter than the typical 9-12 months recommended for extrapulmonary TB, but the patient achieved clinical and microbiological resolution.
- 7. Conclusions:** This case series illustrates the diverse presentations of abdominal TB and the need for a high index of suspicion in endemic areas. Diagnostic confirmation through imaging and microbiological methods is critical. Management requires careful monitoring and may involve adjusting treatment regimens based on patient response and drug tolerance. These cases also underscore the importance of personalized care, including the use of TDM and management of drug-induced adverse effects.

- 8. Recommendations for Clinical Practice:** Maintain a high suspicion for abdominal TB in patients from endemic areas presenting with non-specific abdominal symptoms. Utilize comprehensive diagnostic tools, including imaging and molecular tests like GenXpert, for accurate diagnosis. Consider TDM in cases with suspected drug malabsorption or interactions. Monitor for drug-induced hepatotoxicity, especially in patients receiving standard anti-TB therapy. Individualize treatment plans based on patient response and tolerance, ensuring adherence and monitoring for complications.

This discussion highlights the complexity and nuances in diagnosing and managing abdominal TB, emphasizing the need for a multidisciplinary approach to achieve optimal patient outcomes.

In the case series of Abdominal Tuberculosis (TB), two cases with different clinical presentations were documented and analyzed. Here's a summary covering the clinical, research, evaluation, and management aspects:

Summary

Clinical Presentation

- Case 1:** The patient presented with nonspecific symptoms like abdominal pain, fever, and weight loss. Diagnostic imaging revealed ascites and thickening of the peritoneum, typical signs of peritoneal TB.
- Case 2:** This patient exhibited symptoms of bowel obstruction, including vomiting and abdominal distension. Imaging showed intestinal strictures, which are common in intestinal TB.

Research and Evaluation- Diagnosis: Both cases underwent diagnostic evaluations including imaging studies (ultrasound, CT scans), laboratory tests (including TB-specific tests like Mantoux and IGRA), and biopsy for histopathological examination. In some instances, microbiological cultures or PCR testing confirmed *Mycobacterium tuberculosis*.

Differential Diagnosis: Other conditions like Crohn's disease, malignancies, and other infections were ruled out through comprehensive diagnostic evaluations.

Management

Medical Treatment: Both patients were started on a standard anti-tuberculosis treatment (ATT) regimen, typically including isoniazid, rifampicin, pyrazinamide, and ethambutol for an initial two-month intensive phase, followed by a continuation phase with isoniazid and rifampicin for an additional four months.

Surgical Intervention: In the case of intestinal obstruction, surgical intervention might be considered, especially if there are complications like perforation or severe stricture not responsive to medical therapy.

Follow-up and Monitoring: Regular follow-up was essential to monitor response to therapy, manage potential drug-related side effects, and ensure compliance with the treatment regimen.

Outcomes and Recommendations

Case Outcomes: The response to ATT was positive in both cases, with significant improvement in symptoms and radiological findings. However, long-term follow-up was necessary to monitor for relapse or complications.

Research Insights: The case series highlights the varied presentations of abdominal TB, emphasizing the importance of considering TB in differential diagnoses of abdominal disorders, especially in endemic areas.

Management Recommendations: Prompt diagnosis and treatment are crucial for favorable outcomes. Multidisciplinary management, including gastroenterologists, infectious disease specialists, and surgeons, is often necessary for complex cases.

This summary underscores the need for awareness of abdominal TB's diverse presentations and the importance of a thorough diagnostic approach to ensure appropriate treatment and management.

Message on Abdominal Tuberculosis: Clinical, Social, and Future Perspectives

1. Clinical and Diagnostic Issues Imaging and Diagnosis

Abdominal tuberculosis (TB) often presents with non-specific symptoms, making diagnosis challenging. Advanced imaging techniques, such as ultrasound and CT scans, alongside microbiological testing like GenXpert and FNAC, are crucial for accurate diagnosis. Clinicians must maintain a high index of suspicion, especially in endemic areas, to ensure timely identification and treatment.

Treatment Follow-up and Defaulters: Consistent follow-up is essential in managing abdominal TB due to the prolonged treatment duration and potential side effects. Monitoring liver function tests and adjusting therapy in cases of drug-induced hepatotoxicity are critical. Addressing patient adherence issues, which can lead to treatment default and drug resistance, is vital for successful outcomes.

2. Social and Economic Issues

Stigma of TB: Despite advances in treatment, the stigma associated with TB remains a significant barrier, affecting patients' willingness to seek care and adhere to treatment. Public health efforts should focus on education and reducing stigma to encourage early diagnosis and adherence.

Economic Burden: The cost of prolonged treatment, including the need for hospitalization and specialized diagnostics, can be substantial, particularly in low-income settings. Financial support and social assistance programs are necessary to reduce the economic burden on patients and their families.

3. Future Perspectives

Under-Recognition of Abdominal TB: While pulmonary TB garners significant attention, abdominal TB often goes under-recognized despite its potential severity. Increased awareness, research, and clinical focus on abdominal TB are essential to improve diagnostic rates and treatment outcomes.

Research and Development: Future research should focus on developing more sensitive and specific diagnostic tools

for abdominal TB, as well as exploring shorter, less toxic treatment regimens. Additionally, understanding the pathophysiology and epidemiology of abdominal TB will help in designing targeted interventions.

Public Health Policies: Strengthening public health infrastructure to support TB control, including training healthcare professionals to recognize and manage abdominal TB, is crucial. Policies should also address the social determinants of health, such as poverty and overcrowding, which exacerbate the spread of TB.

Abdominal TB is a significant health issue that requires more clinical attention, public awareness, and research focus. By addressing these challenges, we can improve patient outcomes and reduce the burden of this disease.

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