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Article

Gastrointestinal Disorders in Tuberculosis: Pathogenesis and Modern Approaches

Mamatova Nargiza Toirjonovna[1], Ahtamova Shirin Khayrulloevna[2], Eshtemirov Sarvar Eshmamat Ogli[3], O'ralov Akmal Anvar Ogli[4]

1. Assistant at the Department of Phthisiology and Pulmonology, Samarkand State Medical University
2. Student of medicine Samarkand State Medical University
3. Clinical resident Samarkand State Medical University
4. Clinical resident Samarkand State Medical University

* Correspondence: -

Abstract: Despite a long-standing understanding of the disease, tuberculosis (TB) is still a leading cause of morbidity and mortality globally, with >10 million cases per year and high mortality due to complications. Background: Gastrointestinal (GI) disorders are common in tuberculosis (TB) patients, particularly those with multidrug-resistant (MDR)-TB, and greatly impact treatment adherence and outcomes. Gi complications, albeit clinically relevant, are insuffi ciently integrated into standard clinical care in terms of pathophysiologic mechanisms, diagnostic algorithms, and management of complications16,17. In this review, we analyze the pathogenesis, clinical features, diagnosis and current treatment approaches of tuberculosis associated with gastrointestinal involvement. Gastrointestinal (GI) complications occur via multifactorial mechanisms involving direct mycobacterial infection, systemic inflammation, drug-induced toxicity, dysbiosis, and nutrient deficiencies. The clinical manifestations can vary from dyspepsia and malabsorption to a severe drug-induced hepatitis (Table 1). Biopsy remains the gold standard but diagnostic algorithms integrate biochemical, endoscopic, and imaging modalities. There is an overarching approach based on early identification, monitoring of hepatotoxicity, nutritional support, and multidisciplinary care. This article reviews the currently available evidence on the potency relationship between tuberculosis (TB) treatment and GI health, underscores the notion of a cumulative effect created by the interlinked pathophysiological pathways and suggests integrative approaches considering the synergy for enhanced safety and efficacy. Appropriate interventions for GI complication with all armamentaria will augment compliance with therapy, decrease toxicity, and improve outcome of care in tuberculosis.

Keywords: tuberculosis, drug-induced hepatitis, dysbiosis, malabsorption, nutritional deficiency, intestinal tuberculosis.

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1. Introduction

Tuberculosis has remained one of the most significant infectious diseases over recent decades, exerting a long-term impact on healthcare systems, national economies, and social stability worldwide. According to the World Health Organisation (WHO), more than 10 million new cases of tuberculosis are registered annually, while approximately 1.6 million patients die each year from disease-related complications [1]. One of the leading determinants of unfavourable clinical outcomes remains the toxicity of anti-tuberculosis drug therapy, particularly in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis [2].

While TB treatment can be very damaging to any organ system, the GI tract is one of the organ systems that is most adversely affected. The molecular epidemiology division of WHO has reported that the prevalence of clinically significant gastroenterological

disorders is between 15% and 40% [3], and goes as high as 60% in the MDR/XDR tuberculosis spectrum [4]. These complications often result in treatment interruption, the development of resistant organisms, reduced quality of life and potentially deadly situations such as drug-related hepatitis, life-threatening diarrhea, severe electrolyte disturbances, toxic enteropathy, and nutritional cachexia [5].

The aim of this review is to provide a comprehensive analysis of the mechanisms of gastrointestinal involvement in tuberculosis, their clinical manifestations, diagnostic approaches, and contemporary clinical strategies aimed at reducing toxicity and improving treatment effectiveness.

Pathogenesis of Gastrointestinal Complications

The pathogenesis of GI involvement in tuberculosis is multifactorial and includes direct mycobacterial invasion of digestive organs, drug-induced injury, immunopathological alterations, nutritional deficiencies, dysbiotic changes, and the influence of co-infections most notably HIV and viral hepatitis B and C [6]. Each of these mechanisms can independently shape the clinical picture; however, in routine clinical practice, they usually act synergistically.

2. Materials and Methods

The methodology of this review was designed to enable a global synthesis of contemporary evidence surrounding GI complications in tuberculosis. An approach of a narrative review was employed, with a preference for the peer-review literature, followed by clinical guidelines, and then authoritative reports from the World Health Organization. Methods: Sources were identified via focused searches in PubMed and major medical databases using keywords: tuberculosis, gastrointestinal complications, drug-induced hepatitis, dysbiosis, and nutritional deficiency. We included studies on pathogenesis, clinical features, diagnosis and treatment of gastrointestinal tuberculosis [7]. Through the analysis of observational studies, systematic reviews, and clinical practice guidelines, several paths emerged involving mechanisms including direct mycobacterial invasion, immunoinflammatory responses, drug toxicity, and nutritional deficits common to both the conditions. Clinical diagnostic algorithms were assessed according to laboratory, imaging, and endoscopic modalities and the effect of new and emerging management strategies were reviewed. A multidisciplinary approach including phthisiology, gastroenterology and nutrition was highlighted. The synthesis focused on identifying applicable evidence-based practices and knowledge gaps in current practice, with recommendations that are at least compatible with international standards. Findings were grouped according to the relationship between tuberculosis treatment and the GI outcome to provide a clinically relevant structure conducive to reducing the GI toxicities of tuberculosis management [8].

3. Results and Discussion

1. Direct Mycobacterial Involvement of the Gastrointestinal Tract

Intestinal tuberculosis is the most common form of abdominal tuberculosis and accounts for up to 50–70% of all extrapulmonary GI tuberculosis cases, according to various studies [9]. The most vulnerable sites include the terminal ileum, ileocecal region, cecum, mesenteric lymph nodes, and peritoneum. This predilection is explained by the abundance of lymphoid tissue, delayed intestinal transit, and high absorptive capacity, creating favourable conditions for mycobacterial adhesion and invasion.

Pathogenetically, the disease is characterized by the development of epithelioid granulomas with Pirogov–Langhans giant cells, caseous necrosis, ulceration, fibrotic changes and strictures, along with potential development of gastrointestinal fistulas and mesenteric lymphadenitis [10]. The major importance of this phenomenon is that intestinal tuberculosis mimics Crohn disease in 20–25% of patients, thereby increasing the risk for misdiagnosis and inappropriate immunosuppressive therapy significantly.

Immuno-Inflammatory Mechanisms

Tuberculosis is accompanied by a prolonged systemic inflammatory response. Key cytokines involved in GI tract damage include TNF-α, IL-6, IL-1β, and IFN-γ. Their excessive production leads to impaired intestinal motility, reduced nutrient absorption, increased tissue sensitivity to pharmacological agents, and inflammatory changes in the gastric and intestinal mucosa.

Chronic systemic inflammation promotes anorexia and cachexia, which are considered major risk factors for unfavorable tuberculosis outcomes and an increased incidence of gastroenterological complications [11].

Drug-Induced Toxicity

Virtually all anti-tuberculosis drugs possess some degree of hepato- and gastrotoxicity (Table 1).

Table 1. Drugs posing the greatest risk to the gastrointestinal tract

№	Drug	Type of Toxicity
1	Isoniazid	Hepatitis, nausea
2	Rifampicin	Cholestasis
3	Pyrazinamide	Hepatocyte necrosis
4	Fluoroquinolones	Toxic enteropathy
5	Linezolid	Mitochondrial toxicity
6	Bedaquiline	Dyspepsia, anorexia

Collectively, these effects create a high risk of drug-induced hepatitis and gastrointestinal injury.

Nutritional Deficiency

Studies indicate that up to 80% of patients with tuberculosis suffer from various forms of nutritional deficiency. This is driven by decreased appetite, anorexia, malabsorption, increased energy expenditure due to chronic inflammation, and deficiencies of vitamins D and B12, folic acid, iron, and several trace elements. Nutritional deficiency increases drug toxicity, impairs immune responses, and is associated with higher mortality rates [12].

2. Clinical Manifestations of Gastrointestinal Involvement

Clinical manifestations of GI involvement in tuberculosis can be broadly classified into functional, structural, and toxic forms.

Functional disorders include dyspepsia, epigastric heaviness, nausea, early satiety, and appetite loss. According to several studies, such symptoms occur in 40–60% of patients receiving anti-tuberculosis therapy.

A particularly important complication is drug-induced hepatitis, which develops in 5–25% of patients depending on treatment regimens and pre-existing liver disease. This presents as weakness, pruritus, jaundice, tachycardia, and significant elevations of ALT/AST (5–10×Upper limit of normal). Mechanistically, the disease progresses through several stages: mitochondrial dysfunction, inflammation, cholestasis, and hepatocyte necrosis.

The occurrence of intestinal dysbiosis is high among patients, particularly in the long term use of fluoroquinolones and ethionamide/prothionamide [13]. Symptoms include abdominal distension, diarrhea, increased drunkenness and decreased resistance to gut infection.

Malabsorption and nutritional deficiency manifest as significant weight loss, hypovitaminosis, dry skin, muscle weakness, and anemia, necessitating mandatory nutritional assessment and targeted correction.

3. Diagnosis of Gastrointestinal Involvement

The diagnostic algorithm for suspected GI involvement in tuberculosis should include a combination of laboratory, instrumental, and, when necessary, morphological investigations.

Laboratory evaluation includes assessment of liver function (ALT, AST, alkaline phosphatase, GGT, bilirubin), total protein and albumin, ferritin, serum iron, vitamins D, B12, folate, electrolytes, and coagulation parameters. It is necessary and important for digestion and absorption evaluation that coprological examination is critical.

Recommendation: For patients on linezolid, serum lactate should be measured, and lipase and amylase should be evaluated in suspected cases of pancreatopathy.

Imaging techniques include abdominal ultrasound, esophagogastroduodenoscopy, colonoscopy, computerized tomography (CT), and magnetic resonance imaging (MRI). Steatosis, hepatomegaly, and cholestasis can all be detected via ultrasound. Endoscopic approaches can visualize gastritis, erosions, duodenitis, ulcerations, granulomatous lesions, and strictures. In patients with suspicion of tuberculous peritonitis or abdominal abscesses, CT and MRI demonstrate peritoneal thickening, fibrous septa, and ascites. The gold standard for diagnosis is biopsy of intestinal mucosa or peritoneum, which can identify epithelioid granulomas with caseous necrosis.

4. Drug-Induced Hepatitis as a Key Management Challenge

Drug-induced hepatitis (DIH) is one of the most serious side effects of anti-tuberculosis treatment. Its occurrence is associated with first-line drug toxicity and prolonged treatment strategies for MDR/XDR tuberculosis. Using standard regimens, incidence may vary from 5–25% and the maximum is up to 40% with second-line drugs [14].

While the initial clinical presentation consists of early clinical manifestations (anorexia, right upper quadrant pain, dyspepsia), more severe clinical signs (nausea, vomiting, pruritus, asthenia, tachycardia, dark urine, pale feces), along with life-threatening complications [eg, severe jaundice, impaired prothrombin level, hepatic coma (HE)] may occur. In terms of biochemistry, ALT/AST elevations are 5–10 × upper limit of normal, and there is also increase of bilirubin and alkaline phosphatase, the combined cytolytic–cholestatic patterns also common in MDR tuberculosis (2).

Today, the general guidelines suggest an urgent stop of the most hepatotoxic drugs (pyrazinamide, isoniazid, rifampicin), continuous biochemical controls, detoxification and hepatic cytoprotection if needed, during a subsequent careful and stepwise reintroduction of drugs, after normalisation of the liver tests. In extreme cases, a modification with the exclusion of pyrazinamide and alternative regimens is.

5. Dysbiosis and Intestinal Microbiota Disorders

Prolonged antibiotic therapy, particularly with fluoroquinolones and second-line agents, predictably alters intestinal microbiota composition. Contemporary studies report dysbiosis in 75–80% of tuberculosis patients [15].

Key contributing factors include long-term antibacterial use, low dietary fibre intake, malabsorption, and concomitant intestinal infections. Microbiota disruption leads to reduced local intestinal immunity, increased risk of diarrhea, impaired B-vitamin metabolism, enhanced endogenous intoxication, and reduced drug absorption.

6. Nutritional Deficiency in Tuberculosis Patients

Nutritional deficiency is extremely prevalent and clinically significant in tuberculosis. Up to 80% of patients are underweight, and nearly half exhibit marked hypoproteinemia. This results from the catabolic effects of chronic inflammation, appetite suppression, anorexia, malabsorption, recurrent nausea, vomiting, diarrhea, and psychosocial factors.

Nutritional support should supply 35–40 kcal/kg/day, protein intake 1.2–1.5 g/kg/day, predominance of omega-3 polyunsaturated fatty acids and adequate supplementation of vitamins D, B6, B12, folic acid and trace elements (zinc, selenium) according to WHO-recommendations and clinical studies [3, 4, 5, 6, 7]. These include high-protein formulations (≥20 g protein/serving), omega-3-supplied compounds, and specific nutritional articles for TB-affected clients.

Observational studies demonstrate that adequate nutritional support improves tolerance to anti-tuberculosis therapy, enhances immune status, and reduces the incidence of severe complications.

7. Intestinal Tuberculosis

Abdominal tuberculosis remains one of the most diagnostically challenging forms of the disease. Its clinical presentation often mimics oncological and autoimmune disorders, leading to delayed diagnosis and postponed specific therapy.

Intestinal tuberculosis presents with chronic abdominal pain, anemia, weight loss, diarrhea, stricture formation, and bowel obstruction. Up to 20% of cases are misdiagnosed

as Crohn's disease, particularly in the absence of clear radiological and microbiological evidence of tuberculosis.

4. Conclusion

The review describes a range of gastrointestinal complications with their multifactorial aetiology in tuberculosis as those arising simultaneously from the direct mucosal invasion by mycobacteria, systemic inflammation, drug induced toxicity which is further worsened by dysbiosis and nutritional deficiency as the contributing factors affecting treatment adherence and clinical outcomes. These findings reinforce the integral need for early diagnosis utilizing letter-constituted essential laboratory, imaging, and endoscopic approaches, along with continued and real-time management, such as monitoring for hepatotoxicity and provision of nutritional support. Impact on practice There are important implications for clinical practice in preventing, alleviating and managing these complications to reduce interruptions to therapy and improve patient wellbeing, thus increasing treatment efficacy. Nevertheless, additional studies are necessary to establish standardized protocols to prevent and manage gastrointestinal disorders associated with tuberculosis, investigate the possible role of microbiota modulation, and estimate the long-term effect of nutrition therapy on treatment outcomes.

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