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Challenging Diagnosis of Intestinal Tuberculosis: A Review

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ABSTRACT

Intestinal tuberculosis (ITB), a subset of extrapulmonary tuberculosis (EPTB), arises from *Mycobacterium tuberculosis* infection, primarily affecting the ileocecal region due to its lymphatic tissue richness. Representing approximately 10% of global EPTB cases, ITB is most prevalent in regions with high tuberculosis (TB) incidence. Its nonspecific symptoms - abdominal pain, diarrhea, fever, and weight loss - pose significant diagnostic challenges and frequently overlap with conditions like Crohn's disease (CD). This diagnostic complexity is compounded by shared clinical, endoscopic, and histological features, with misdiagnosis risking inappropriate immunosuppressive therapy that exacerbates TB progression.

Diagnostic tools include endoscopy with biopsy, imaging modalities (CT, MRI, ultrasound), and molecular assays like GeneXpert for rapid detection and drug resistance assessment. While histological markers such as caseating granulomas aid differentiation, advanced molecular methods enhance diagnostic precision. Emerging technologies, including next-generation sequencing, CRISPR-based diagnostics, and artificial intelligence in imaging, show promise in addressing diagnostic gaps. However, resource-limited settings face significant barriers, relying on less sensitive conventional methods.

Integrated approaches combining clinical, histopathological, and molecular evaluations are essential for accurate diagnosis and effective management. Strengthening healthcare infrastructure, expanding access to advanced diagnostics, and leveraging innovative technologies are critical for reducing ITB-related morbidity and mortality.

Keywords: Intestinal tuberculosis, Diagnostic challenges, Molecular diagnostics, Artificial intelligence, GeneXpert.

INTRODUCTION

Tuberculosis, caused by *Mycobacterium tuberculosis*, is primarily a pulmonary disease; however, it can spread beyond the lungs to involve other organs, leading to extrapulmonary tuberculosis (EPTB). EPTB includes lymphatic, genitourinary, skeletal, and gastrointestinal tuberculosis. These manifestations account for up to 15-20% of all TB cases, with intestinal tuberculosis making up approximately 10% of EPTB cases globally. EPTB's atypical symptoms and non-specific signs often lead to delayed diagnosis, posing unique challenges compared to pulmonary TB.

Intestinal tuberculosis (ITB) is a form of EPTB affecting the gastrointestinal tract. The ileocecal region is the most commonly affected site due to its lymphatic tissue abundance. ITB often arises when TB

bacteria spread from pulmonary infections via hematogenous or lymphatic routes, or by ingestion of infected sputum. Symptoms include abdominal pain, diarrhea, fever, and weight loss, often mimicking other gastrointestinal conditions, which complicates diagnosis and treatment.

Intestinal tuberculosis remains a significant health concern, especially in areas with high TB prevalence like parts of Asia and Africa. Its diagnosis is challenging due to non-specific symptoms and overlap with other conditions like Crohn's disease (CD). Conventional diagnostic methods like sputum cultures, biopsies, and imaging often have low sensitivity for ITB, requiring the integration of molecular diagnostics and advanced imaging techniques to improve accuracy.

Accurate diagnosis of ITB is crucial for appropriate treatment and to avoid the complications associated with untreated or misdiagnosed cases. Proper diagnosis helps to guide anti-tubercular therapy, which is essential for preventing progression and complications such as intestinal obstruction, perforation, or chronic malabsorption, which can have severe outcomes.

ITB and Crohn’s disease share overlapping clinical, endoscopic, and histological features, often leading to misdiagnosis. Incorrectly diagnosing Crohn’s disease instead of ITB can lead to inappropriate use of immunosuppressive therapies, worsening the TB infection. This misdiagnosis has serious health implications and underscores the need for differential diagnostic approaches to distinguish between these conditions.

A timely and accurate diagnosis of ITB is essential to prevent serious complications and ensure effective treatment. Misdiagnosis, particularly confusion with Crohn's disease, can lead to inappropriate treatments, such as immunosuppressive therapies, which can worsen TB and cause further dissemination of the infection. Diagnostic methods have traditionally included histopathology, tissue cultures, and newer polymerase chain reaction (PCR)-based methods like GeneXpert, which increase accuracy by identifying drug-resistant strains and confirming TB quickly. Improving diagnostic specificity is vital to mitigate the risks associated with misdiagnosis and to improve patient outcomes. Given the morbidity and potential for life-threatening complications, timely and precise diagnostic methods for ITB are critical. The use of newer molecular techniques (such as PCR-based tests) alongside traditional diagnostic methods can enhance sensitivity and specificity, leading to better outcomes through targeted treatment. Improved diagnostic accuracy can reduce unnecessary treatment for non-tuberculous conditions and improve patient prognosis [1 – 3].

CLINICAL CHALLENGES IN DIAGNOSING INTESTINAL TUBERCULOSIS:

Overlap with Other Gastrointestinal Conditions:

ITB often overlaps with other gastrointestinal diseases, which complicates its diagnosis. ITB shares a significant clinical overlap, particularly with CD. Both diseases affect the ileocecal area, resulting in inflammation, thickening, and ulceration of the bowel wall. This overlap complicates diagnosis since both diseases may present with similar endoscopic findings, including ulcerations and strictures. ITB may also present with mass lesions, mimicking neoplasms, especially in regions where tuberculosis is endemic.

ITB and CD exhibit similar symptoms, including abdominal pain, diarrhea, fever, and weight loss. In CD, however, skip lesions (discontinuous areas of inflammation) are more common, while ITB often involves continuous segments of the bowel. Cancers and infections can also present with these symptoms, especially in cases where there is colonic involvement or mass formation, making it difficult to distinguish ITB from malignancies without biopsy and histological examination. Common symptoms are abdominal pain,

weight loss, diarrhea, fever, and mass lesions. Patients with ITB typically present with abdominal pain, weight loss, diarrhea, fever, and sometimes visible or palpable abdominal masses. These symptoms, though characteristic, are also common in a range of gastrointestinal disorders, contributing to diagnostic complexity.

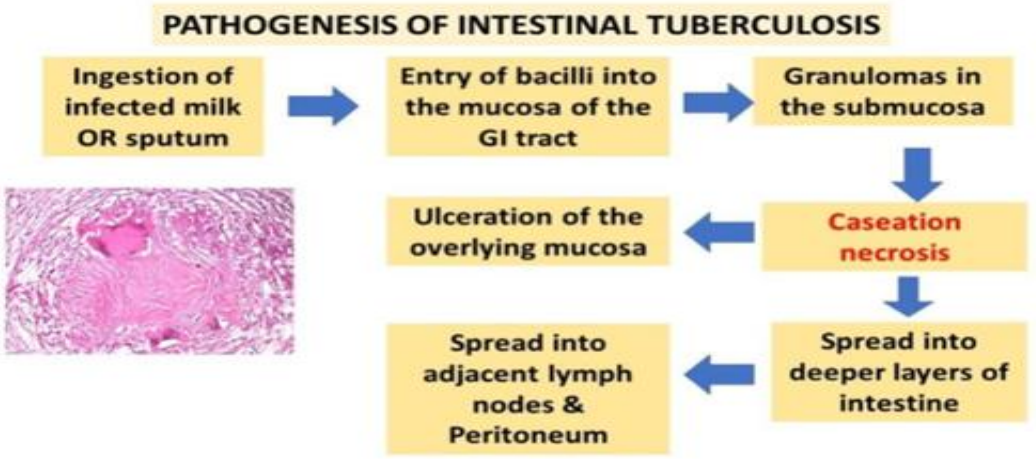

Figure 1: Pathogenesis of Intestinal Tuberculosis

Non-Specificity of Symptoms and Clinical Presentation:

The nonspecific nature of ITB symptoms, such as generalized abdominal discomfort and systemic symptoms like fever and weight loss, limits the ability to rely on clinical presentation alone for diagnosis. This non-specificity necessitates the use of imaging and histological analysis to achieve accurate diagnosis, especially since symptoms like abdominal pain and diarrhea could indicate a range of infections or inflammatory conditions. Additionally, the clinical presentation of ITB is broad, varying from mild and nonspecific symptoms to severe and localized issues, which can mislead clinicians. Unlike pulmonary TB, ITB may not display hallmark features, complicating diagnosis further. The non-specificity of symptoms also means that conditions like gastrointestinal cancer, which can present with similar pain or mass formations, are often considered in differential diagnosis. Factors influencing this variability include immune status, coexisting conditions, and the specific area of intestinal involvement.

The wide spectrum of clinical presentations that complicate diagnosis:

ITB can have a wide range of presentations, from mild symptoms resembling irritable bowel syndrome to severe complications like bowel obstruction or perforation. Factors such as patient immunity, disease duration, and concurrent infections influence the diversity of presentations, contributing to the challenges of timely diagnosis. In some cases, patients might present with more acute and pronounced symptoms, while others may show more chronic, nonspecific signs. The wide spectrum of clinical manifestations in ITB can present either as typical forms, such as localized inflammation and caseating granulomas (typical for TB), or atypical forms, like non-caseating granulomas, which are also seen in Crohn's disease. Imaging findings may show inflammation or thickening in the ileocecal region, which could resemble inflammatory bowel disease, especially Crohn's. This overlap extends to endoscopic findings, where similar ulcerations or segmental involvement can be seen, leading to diagnostic ambiguity. Histologically, the presence of necrotic and non-necrotic granulomas may indicate ITB, but in some cases, only specific TB tests like acid-fast bacilli (AFB) staining or PCR can conclusively identify the disease.

Typical vs. Atypical presentations and factors influencing clinical diversity:

The variability in clinical presentations is influenced by factors such as disease duration, host immune response, and co-existing conditions. For example, while Crohn's disease may involve any segment of the gastrointestinal tract in a discontinuous "skip" pattern, ITB often affects the ileocecal area, sometimes leading to complications like obstruction or abscesses if untreated. Accurate diagnosis is essential because treating ITB as Crohn's disease with immunosuppressants could worsen the patient's condition due to the progression of the undiagnosed infection. While most cases of ITB show classic signs in the ileocecal region, atypical presentations involving other parts of the gastrointestinal tract can also occur. Such variability further complicates diagnostic efforts and may lead to missed diagnoses if clinicians are not aware of the full range of potential presentations. Factors influencing this clinical diversity include immune status, duration of symptoms, and whether the patient has received prior treatments, such as corticosteroids, which can mask or alter disease manifestation. Accurate diagnostic methods such as endoscopy, biopsy, and molecular tests are crucial but may be inaccessible in some regions, increasing the risk of misdiagnosis [4 – 7].

DIAGNOSTIC METHODS FOR INTESTINAL TUBERCULOSIS:

1. Endoscopic and Biopsy-Based Methods

Endoscopy, particularly colonoscopy, is a primary diagnostic tool for ITB. Biopsies are obtained during endoscopic exams for histopathological analysis, where features like granulomas and acid-fast bacilli may be detected. However, biopsy results can be inconclusive due to patchy tissue involvement or sampling errors. Colonoscopy allows direct visualization of the gastrointestinal tract and helps identify areas affected by ITB. Commonly examined sites include the terminal ileum and ileocecal region, where tuberculosis-related lesions are typically found. Colonoscopy can also guide biopsy sampling from these areas to increase diagnostic yield. Typical endoscopic findings in ITB include ulcers (often transverse or irregular), strictures, nodules, mucosal thickening, and inflammatory masses. These findings are particularly frequent in the ileocecal region, which is commonly affected by ITB. Such features may help differentiate ITB from other conditions, though they are not entirely specific. Despite its utility, endoscopic and biopsy methods have limitations. Sampling errors and the focal nature of ITB can lead to false negatives. Additionally, the similarity between ITB and Crohn's disease makes histopathological interpretation challenging, often requiring additional molecular diagnostics to confirm Mycobacterium tuberculosis presence and improve diagnostic accuracy. These diagnostic challenges emphasize the need for comprehensive methods combining endoscopy, biopsy, and molecular testing to achieve accurate ITB diagnosis [4, 6, 8].

2. Imaging Techniques

Imaging plays a critical role in diagnosing ITB and assessing the extent of the disease. CT, MRI, and ultrasound are commonly used, each providing unique benefits depending on availability and clinical needs. CT scans are generally preferred for their detail, while MRI offers higher contrast for soft tissues, though less accessible in many settings. These techniques help detect bowel wall abnormalities, lymphadenopathy, and ascites, aiding in diagnosis and differentiation from other gastrointestinal diseases.

CT - Scan and MRI: CT scans are particularly effective for detecting characteristic signs of ITB, such as concentric wall thickening, lymph node enlargement, and caseating granulomas. MRI offers high-resolution images that highlight soft tissue contrast and is useful for detecting inflammation, bowel wall thickening, and peritoneal involvement.

Both imaging methods are highly beneficial in assessing disease severity and complications like strictures or perforations.

Ultrasound: In resource-limited settings, ultrasound is a practical option for evaluating ITB. Though less specific than CT or MRI, ultrasound can detect signs like bowel wall thickening and lymphadenopathy, especially in early disease stages. It is a non-invasive, affordable alternative and can serve as a first-line imaging tool where CT or MRI is unavailable.

Challenges in Imaging: Despite the utility of imaging, overlap exists between ITB and conditions like Crohn's disease or malignancies, often leading to diagnostic challenges. Expertise in recognizing specific imaging patterns of ITB is essential to distinguish it from these diseases accurately. CT and MRI findings can be similar in appearance across different conditions, making it difficult to establish a definitive diagnosis without supportive histopathology [1, 4].

3. Histopathology

The primary histopathological markers for ITB are caseating granulomas with central necrosis and Langhans giant cells. These features are typically found in granulomatous inflammation, particularly in the ileocecal region. The granulomas in ITB are often large and confluent, contrasting with the smaller, well-defined granulomas of CD, which rarely show necrosis. The presence of these histological markers can suggest ITB, especially if AFB are detected using special stains like Ziehl-Neelsen.

The sensitivity of biopsy in diagnosing ITB is limited, especially in small tissue samples, due to the inconsistent presence of AFB and the potential for non-caseating granulomas in some ITB cases. Additionally, non-caseating granulomas can appear in CD and other inflammatory conditions, which reduces specificity. As a result, pathologists often struggle to conclusively diagnose ITB from biopsy alone without corroborating clinical and laboratory data.

Histological similarities with CD add to the challenge, as both conditions can show granulomatous inflammation. Although ITB typically has larger, caseating granulomas and involves lymph nodes with necrotic features, these distinctions are not always clear, and biopsy interpretation requires significant expertise. Molecular testing (e.g., PCR for Mycobacterium tuberculosis DNA) may be employed to increase diagnostic accuracy, especially in cases with ambiguous histological findings [9 - 11].

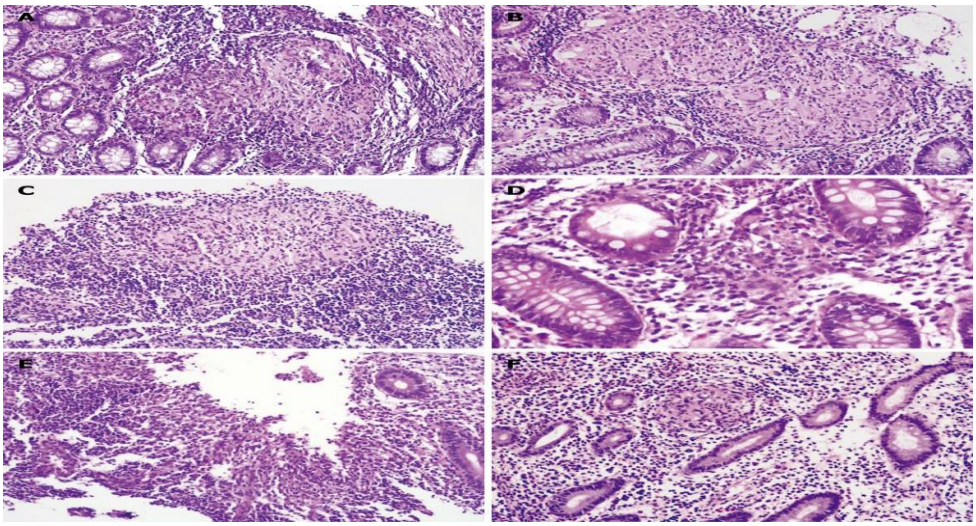

Figure 2: Histopathological differences between Intestinal Tuberculosis (ITB) and Crohn's Disease (CD). ITB: (A) Presence of confluent granulomas; (B) Confluent granulomas with caseous necrosis and Langhans giant cells; (C) Granulomas surrounded by lymphoid cuff; (E) Band of epithelioid histiocytes observed at the base of ulcers. CD: (D) Vague or poorly defined granulomas; (F) Small granulomas, often sparse and scattered [12].

4. Microbiological Tests

Culture and Staining: Acid-fast bacilli (AFB) staining is specific but has low sensitivity in tissue samples, often missing cases due to the scarcity of bacilli in ITB. The culture, regarded as a diagnostic gold standard, is highly specific but takes time (up to six weeks) and requires optimal sample collection.

Mycobacterial Cultures: Although cultures provide definitive diagnosis and drug susceptibility data, they have a long turnaround time and sometimes yield false negatives if the sample size or quality is insufficient. Rapid growth cultures like the MGIT system reduce time to detection, but may still take several days.

Molecular Diagnostics: PCR-based tests, such as GeneXpert, offer rapid and reliable detection of Mycobacterium tuberculosis and rifampicin resistance within hours. GeneXpert is highly valued for its speed and utility, particularly in low-resource settings, though sensitivity in paucibacillary cases can vary. It is valuable as it detects both tuberculosis and rifampicin resistance in hours, offering faster results compared to traditional methods. Despite high sensitivity, GeneXpert's performance varies in different gastrointestinal samples [2, 13].

Limitations: Despite their benefits, PCR and GeneXpert can be cost-prohibitive in resource-limited areas. Sensitivity and specificity are also variable, with false positives or negatives possible, depending on sample type and bacterial load. Combining multiple diagnostic methods often improves overall diagnostic accuracy for ITB [2].

5. Immunological and Serological Tests

Interferon Gamma Release Assays (IGRAs)

IGRAs are blood tests, including the QuantiFERON-TB Gold and T-SPOT.TB, which measures the immune system's response to Mycobacterium tuberculosis antigens. They detect the release of interferon-gamma (IFN-γ) when T-cells are exposed to TB-specific antigens. A significant benefit of IGRAs is that, unlike tuberculin skin tests, they are unaffected by the BCG vaccine, making them more reliable for individuals previously vaccinated against TB. However, IGRAs have limitations: while they effectively identify latent TB infections, they do not distinguish between latent and active TB, which complicates their use for diagnosing ITB specifically. Additionally, IGRAs may have variable sensitivity in immunocompromised patients or those with early-stage infections, potentially leading to false-negative results in such cases.

Serological Markers

Serological tests attempt to identify antibodies or antigens associated with Mycobacterium tuberculosis in the bloodstream. However, their role in ITB diagnosis is limited due to inconsistent sensitivity and specificity. False positives can occur because some antibodies are present in non-TB mycobacterial infections or other conditions, leading to a lack of reliability. Consequently, serological markers are not typically recommended for routine ITB diagnosis and are generally reserved for specific research or supplemental diagnostics rather than frontline diagnostic use [14 - 16].

6. New and Emerging Diagnostic Methods

Emerging diagnostics are centered on molecular techniques and biomarker discovery, which offer rapid, specific detection of Mycobacterium tuberculosis. Among these, next-generation sequencing and CRISPR-based diagnostics are making notable strides. These technologies provide a faster, more comprehensive understanding of tuberculosis DNA, enabling the identification of mutations related to drug resistance and potentially improving tailored treatment for patients

Molecular Techniques: Next-Generation Sequencing and CRISPR-Based Diagnostics

- **Next-Generation Sequencing (NGS):** NGS, especially whole genome sequencing (WGS), enables high-resolution detection of Mycobacterium tuberculosis mutations and helps clinicians understand bacterial resistance mechanisms, which is crucial for effective treatment. While highly accurate, WGS requires specialized laboratory setups, making it challenging to implement in low-resource settings. Targeted NGS, which sequences specific genes associated with drug resistance, is also being explored as a faster, more accessible option.
- **CRISPR-Based Diagnostics:** CRISPR technology, particularly with CRISPR-Cas systems, allows rapid, targeted detection of tuberculosis DNA sequences. While still under research, CRISPR-based diagnostics have shown the potential to enhance sensitivity and specificity in TB detection, including in extrapulmonary cases like ITB. However, CRISPR diagnostics for ITB are still emerging and require further development for widespread use.

Biomarkers: Promising Candidates Under Study

Research into specific biomarkers for ITB aims to identify blood or tissue markers that correlate with tuberculosis infection. Biomarkers such as cytokines (e.g., IFN-γ), and proteins released by infected cells are under study for their ability to differentiate TB from other inflammatory gastrointestinal conditions. While still experimental, biomarker research could lead to quicker, non-invasive diagnostic tests that are more specific to ITB, but many of these biomarkers are yet to reach clinical validation [2, 17 – 21].

DIFFERENTIAL DIAGNOSIS WITH CROHN'S DISEASE:

ITB and CD share many clinical presentations, such as abdominal pain, diarrhea, weight loss, fever, and bowel obstruction, making them challenging to distinguish based solely on symptoms. Histopathologically, both conditions can exhibit granulomas, inflammation, and ulcerations. However, caseating granulomas (with necrosis) are more specific to ITB, though they are not always present, and CD can also show granulomas without necrosis, adding to the complexity.

Similarities and Differences in Symptoms and Endoscopic Findings

Symptoms such as fever and night sweats are more commonly associated with ITB. Endoscopically, ileocecal involvement is typical for both diseases, but CD often shows a "skip lesion" pattern (patchy inflammation), whereas ITB lesions tend to be more continuous. The presence of lymph nodes with central necrosis and transverse ulcers are characteristic of ITB, which can aid in its differentiation from CD when observed through imaging and endoscopy.

Table 1: CT scan findings of Intestinal Tuberculosis and Crohn's Disease [22]

Features	Intestinal Tuberculosis (ITB)	Crohn's Disease (CD)
Mural thickening	Homogenous thickening without stratification	Stratified thickening in active inflammation
Strictures	Typically, concentric	Often eccentric
Fibrofatty Proliferation	Very rare	Commonly observed
Mesenteric Inflammation	Present, but without vascular engorgement	Associated with hypervascularity (comb sign)
Lymph Nodes	Hypodense lymph nodes with rim enhancement	Mild lymphadenopathy
Ascites/Abscesses	High-density ascites	Abscess formation

Table 2: Colonoscopic findings of Intestinal tuberculosis and Crohn's disease [23]

Features	Intestinal Tuberculosis (ITB)	Crohn's Disease (CD)
Ulcers	Transverse ulcers (e.g., caecal, ascending colonic, or transverse colon)	Apthous ulcers in terminal ileum; deep longitudinal or serpiginous ulcers
Lesion Distribution	Skip lesions with distorted, ulcerated, and narrowed caecum	Multiple small ulcers; cobblestoning pattern with deep intervening ulcers
Caecum Involvement	Commonly involved; distorted, narrowed, and ulcerated with a gaping ileocecal valve	May involve the ileocecal valve but less specific narrowing than ITB
Pseudopolyps	Pseudopolyp-like lesions in treated cases; may progress to narrowing requiring surgery	Associated with deep ulcers and cobblestoning; less narrowing compared to ITB
Cobblestoning	Rarely observed	Prominent, with deep ulcers in between
Other Findings	High likelihood of isolated caecal and ascending colonic involvement	Left-sided colonic ulcers of varying sizes; ileitis with small apthous ulcers

Diagnostic Criteria for Differentiation

Several criteria help in differentiating these diseases, including imaging, histopathology, and molecular tests. For instance, CT enterography can be insightful; CD commonly shows left colon involvement, an asymmetric pattern of bowel wall thickening, and the "comb sign" (engorged vasa recta). ITB, however, tends to display lymph nodes with central necrosis, ileocecal valve contracture, and ascites. Additionally, ITB is often accompanied by positive tuberculosis skin tests and may show pulmonary TB signs on imaging, while these are absent in CD.

Key Distinguishing Features in Imaging, Histopathology, and Molecular Markers

Radiological findings can provide important distinctions. CT and MRI are effective in identifying bowel wall characteristics unique to each condition. Histologically, ITB is more likely to exhibit caseating granulomas and Langhans giant cells, though these features can sometimes overlap. Molecular diagnostics, including PCR for Mycobacterium tuberculosis, offer enhanced specificity but are not universally available or definitive due to variable sensitivity.

Role of Combined Diagnostic Approaches

Given the overlapping features, a combined approach involving clinical, endoscopic, histological, and molecular methods is beneficial for improving diagnostic accuracy. Using multiple modalities can help rule out or confirm the presence of specific features linked to ITB or CD, thereby reducing misdiagnosis. This integrated approach enhances diagnostic specificity and can help avoid unnecessary treatments or delays in appropriate therapy.

Benefits of Using Multiple Diagnostic Methods

By using a combination of diagnostic tools, clinicians can more accurately diagnose ITB versus CD, reducing misdiagnosis risks. This approach minimizes the likelihood of unnecessary anti-TB treatment in CD patients or immune suppression in ITB patients, ultimately improving patient outcomes [11, 24, 25].

DIAGNOSTIC ALGORITHMS AND BEST PRACTICES FOR CLINICIANS:

Current Diagnostic Algorithms for ITB

Diagnostic algorithms for ITB often begin with a comprehensive clinical evaluation, including a detailed patient history and physical examination. It's critical to consider the possibility of ITB, especially in regions with high TB prevalence. Patients with symptoms such as unexplained fever, weight loss, diarrhea, abdominal pain, and masses are prioritized for further workup. These clinical clues are followed by imaging studies, endoscopy, biopsy, microbiological tests, and molecular assays.

Step-by-step approach:

- **Clinical evaluation:** Initial assessment focuses on identifying risk factors (e.g.,

immunosuppression, travel to endemic regions).

- **Imaging:** CT scans or MRIs help identify characteristic findings like wall thickening or abscess formation.
- **Endoscopy & Biopsy:** Colonoscopy and laparoscopy allow direct visualization and tissue sampling for histopathological analysis.
- **Microbiological tests:** PCR-based assays and culture tests aim to confirm the presence of Mycobacterium tuberculosis.
- **Molecular diagnostics:** Tools like GeneXpert can rapidly identify the pathogen.

Review of Guidelines and Workflows

International guidelines recommend that clinicians approach suspected ITB using a combination of clinical, radiological, and microbiological criteria. Notably, the World Gastroenterology Organisation (WGO) and European Crohn's and Colitis Organization (ECCO) emphasize the importance of differentiating ITB from other gastrointestinal diseases like Crohn's disease through a careful diagnostic process. Diagnostic accuracy is enhanced by including multiple biopsy sites and considering therapeutic trials in cases where uncertainty persists.

Importance of Clinical Judgment

The role of clinical experience cannot be overstated, especially in endemic areas. Misdiagnosis or delayed diagnosis can lead to inappropriate treatment, such as administering steroids for suspected Crohn's disease instead of initiating anti-tuberculosis therapy. This emphasizes the need for heightened clinical awareness in areas where both ITB and CD are prevalent. Endoscopy and biopsy results often show similar histopathological features, and imaging findings can be ambiguous. Therefore, expertise and experience in interpreting these diagnostic results are crucial, particularly in low-resource settings where advanced techniques might not be available [4, 26, 27].

CHALLENGES IN LOW-RESOURCE SETTINGS:

In low-resource settings, the diagnosis of ITB faces several significant challenges due to the limitations in access to advanced diagnostic tools. One major issue is the lack of availability of specialized tests, such as molecular diagnostics (e.g., PCR) and automated systems (e.g., GeneXpert) for rapid tuberculosis detection. These tests, which are crucial for quick and accurate diagnosis, often remain inaccessible due to high costs and insufficient infrastructure in resource-constrained environments.

In such settings, healthcare providers are often forced to rely on basic diagnostic methods, which may include clinical evaluations and basic imaging (e.g., ultrasound) that may not be sensitive or specific enough to diagnose ITB conclusively. In addition, the use of less expensive and more accessible techniques, such as AFB staining and sputum culture, is common; however, these methods often have low sensitivity in detecting ITB, particularly when the disease manifests outside the lungs.

For regions with limited resources, alternative approaches may include a focus on symptom-based diagnosis and the reliance on available imaging techniques, which the clinical presentation of the disease can supplement. Symptoms such as abdominal pain, weight loss, diarrhea, and fever—commonly associated with ITB—often overlap with those of other gastrointestinal conditions, complicating the diagnosis. Therefore, a combination of clinical suspicion, basic imaging, and potentially histopathological evidence remains a critical component of diagnosis, although this also presents challenges in interpretation without advanced tools.

Improving diagnostic capacity in low-income areas is vital not only to ensure the timely and accurate identification of ITB but also to reduce the overall burden on public

health systems. Investment in strengthening healthcare infrastructure—such as by expanding access to molecular testing, enhancing training for healthcare workers, and promoting early detection—is essential. Addressing these diagnostic gaps could help reduce the incidence of misdiagnoses and ensure more effective treatment outcomes, ultimately alleviating the strain on both individuals and health systems [2, 7, 28].

FUTURE DIRECTIONS IN ITB DIAGNOSIS:

Advancements in Molecular and Genetic Testing: Molecular and genetic testing for TB has advanced significantly in recent years. Techniques like PCR and loop-mediated isothermal amplification (LAMP) are now used to detect Mycobacterium tuberculosis with higher sensitivity and specificity compared to traditional methods. Molecular assays, such as the GeneXpert MTB/RIF, are particularly promising for identifying drug-resistant TB in real time. These advances have revolutionized TB diagnostics, particularly in cases of extrapulmonary TB like ITB, where traditional methods may not be as effective.

Emerging Technologies for Rapid and Accurate Results: Several emerging technologies promise to enhance TB diagnosis. NGS offers high-throughput analysis, which could allow for rapid detection and characterization of TB strains, including drug resistance profiles. Furthermore, CRISPR-based diagnostic tools are being explored for their potential to provide rapid, highly sensitive diagnostics at the point of care. These technologies could dramatically shorten diagnostic timelines, especially in regions with a high TB burden.

Potential for Artificial Intelligence in Diagnostic Imaging: Artificial intelligence (AI) is playing an increasing role in the diagnostic process, particularly in radiology. AI algorithms, especially deep learning models, have shown great promise in improving the accuracy of chest X-rays and CT scans for detecting TB, including its extrapulmonary forms such as ITB. AI models trained on large datasets can help identify patterns in radiologic images that might be missed by human eyes, increasing diagnostic accuracy and reducing time to treatment.

Role of AI in Enhancing Accuracy in Radiology and Endoscopy for ITB: In addition to imaging, AI is also being integrated into diagnostic procedures like endoscopy. AI-assisted endoscopic techniques can help detect abnormalities in the gastrointestinal tract, including lesions or narrowing typical of ITB, which can be challenging to distinguish from other diseases like Crohn's disease. The application of AI in these areas holds the potential to greatly enhance diagnostic precision, reducing misdiagnosis and ensuring timely treatment.

Need for Better Biomarkers: The identification of specific biomarkers for ITB remains a key area of research. Currently, serological markers are not highly specific for TB and often fail to distinguish it from other conditions like Crohn’s disease or cancer. Ongoing studies are focusing on discovering biomarkers that are specific to ITB, which could improve diagnosis and offer better prognostic indicators. Biomarker research is also targeting host immune responses, which might offer insights into the presence of TB even in the absence of detectable mycobacteria.

Ongoing Research into Specific Biomarkers for ITB: Research into biomarkers for ITB is still in its early stages. However, promising candidates are being explored, including proteins involved in immune responses, such as cytokines and specific T-cell markers. Researchers are also investigating the potential of genetic signatures specific to M. tuberculosis infection in the gut. These biomarkers could lead to quicker, less invasive diagnostic tests that complement traditional imaging and microbiological methods [29, 30].

CONCLUSION

Intestinal tuberculosis, an extrapulmonary manifestation of Mycobacterium tuberculosis, poses significant diagnostic challenges due to its clinical overlap with other gastrointestinal conditions such as Crohn's disease and malignancies. Its nonspecific symptoms, ranging from abdominal pain and diarrhea to weight loss and fever, often delay diagnosis. The ileocecal region is most commonly affected, necessitating advanced diagnostic methods like endoscopic biopsies, imaging techniques, and molecular assays such as PCR and GeneXpert to improve accuracy. Misdiagnosis can lead to severe complications, including inappropriate immunosuppressive therapy, and worsening TB progression. Emerging technologies like next-generation sequencing, CRISPR-based diagnostics, and artificial intelligence in imaging offer hope for more precise and timely diagnoses. However, low-resource settings face barriers due to limited access to these advanced tools. A multidisciplinary approach combining clinical evaluation, imaging, histopathology, and molecular diagnostics is vital to distinguish ITB from other conditions effectively. Strengthening healthcare infrastructure and integrating innovative diagnostics are critical to improving outcomes for ITB patients globally.

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