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TUBERCULOSIS: CHALLENGES IN DETECTION AND TREATMENT ADHERENCE

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Abstract: Tuberculosis (TB) remains a critical global public health challenge, sustained by a vast reservoir of latent infection and high morbidity and mortality rates. This narrative review analyzes the main obstacles to controlling the disease, focusing on the difficulties of detection and adherence to treatment. Diagnosis is hampered by the limitation of current immunological tests (TST and IGRA) in differentiating latent infection from active disease, as well as the complexity of identifying paucibacillary forms in children and extrapulmonary presentations, such as spinal and miliary TB. In the therapeutic sphere, the long duration of traditional regimens is the main barrier to adherence. The study highlights the importance of transitioning to shorter and safer regimens (based on rifamycins) for the treatment of latent infection and the need for appropriate pediatric formulations. The analysis reinforces that overcoming these challenges requires diagnostic innovation and patient-centered therapeutic strategies.

Keywords: Tuberculosis; Diagnosis; Treatment Adherence; Mycobacterium tuberculosis; Latent Infection; Preventive Therapy; Public Health.

INTRODUCTION

Tuberculosis (TB), caused by mycobacteria of the *Mycobacterium tuberculosis* complex (Jaganath et al., 2022; Kwas et al., 2024), remains a critical public health challenge on a global scale (Kwas et al., 2024; Matteelli et al., 2022). The World Health Organization (WHO) estimates that the reservoir of infection (TBI) reaches 1.7 billion people, constituting the source of future cases of the disease (Matteelli et al., 2022).

Despite control efforts, TB continues to present high morbidity and mortality (Kwas et al., 2024), affecting millions of individuals annually, including a significant burden on children (Jaganath et al., 2022).

Effective control of the disease faces two main obstacles. The first is diagnostic difficulty; detecting TB, especially in its miliary, spinal, or pediatric forms, can be complex, nonspecific, and challenging even for experienced clinicians (Jaganath et al., 2022; Kwas et al., 2024; Na et al., 2023). The second challenge lies in treatment adherence, where the long duration of traditional treatment regimens for both latent infection and active disease results in low completion rates (Jaganath et al., 2022; Matteelli et al., 2022). This review aims to analyze the current challenges in TB detection and discuss therapeutic strategies focused on improving treatment adherence.

METHODOLOGY

This study is a narrative review of the literature, whose purpose is to analyze and synthesize current scientific evidence on the challenges in the diagnosis and treatment of tuberculosis. The bibliographic search was conducted in the PubMed database. The descriptors "Tuberculosis," "treatment," and "diagnosis" were used, according to the terminology of the Medical Subject Headings (MeSH) of the Medical , combined with the Boolean operators AND and OR to refine the search.

The inclusion criteria defined for the selection of studies were: articles published in the last five years, available for reading in full, and written in English, French, or Portuguese, which directly addressed the proposed topic. Studies that were not directly relevant to the central theme, duplicate publications, other narrative reviews with low methodological rigor, and articles not indexed in the database consulted were excluded. The selection of articles took place in two distinct phases: initially, a screening based on titles and abstracts and, subsequently, a complete reading of the texts to validate their relevance. The data were extracted and compiled in a descriptive manner.

RESULTS AND DISCUSSION

Effective tuberculosis management requires overcoming significant barriers in both diagnosis and treatment adherence. Diagnostic challenges are multifaceted, ranging from the inability of current tests to differentiate latent infection from active disease to the difficulty in identifying atypical forms of the disease (Goletti et al., 2022; Na et al., 2023). In the therapeutic sphere, the main obstacle remains the long duration of treatment regimens, which directly impacts patient adherence (Jaganath et al., 2022).

Challenges in Tuberculosis Detection

The diagnosis of TB is often hampered by clinical polymorphism and the lack of a single, definitive test (Kwas et al., 2024). A central challenge is the limitation of available immunological tests, such as the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs). Both methods diagnose TB infection (TBIs) by measuring the host's immune response to *M. tuberculosis* antigens, but they are unable to distinguish

between active disease and controlled latent infection (Goletti et al., 2022; Jaganath et al., 2022).

The main limitation of these tests is their low positive predictive value (PPV) for the progression of infection to active disease, estimated at less than 10% (Goletti et al., 2022; Matteelli et al., 2022). In practice, this implies that a large number of individuals need to receive preventive therapy (PT) to prevent a single case of TB, which complicates public health decisions (Matteelli et al., 2022).

In pediatrics, the challenge is even greater. Diagnosis in children is hampered by the paucibacillary nature of the disease (low bacilli load), which drastically reduces the sensitivity of traditional microbiological tests, such as smear microscopy and sputum culture (Jaganath et al., 2022). In addition, the immature immune system of young children can lead to a higher proportion of false-negative or indeterminate results in IGRA (Goletti et al., 2022; Jaganath et al., 2022). Although molecular tests (NAATs), such as Xpert MTB/RIF, have improved sensitivity in respiratory and non-respiratory samples (such as stool), there is no single test that can reliably diagnose pediatric TB (Jaganath et al., 2022).

Extrapulmonary forms also present diagnostic difficulties. Spinal tuberculosis (Pott's disease), for example, can mimic neoplastic lesions or metastases, especially in its atypical "non-contiguous" forms (skipped lesions), where the vertebrae are affected without involvement of the adjacent intervertebral disc (Na et al., 2023). In these cases, magnetic resonance imaging (MRI) is the test of choice, but definitive diagnosis often requires biopsy and histopathological analysis (Na et al., 2023). In miliary TB, characterized by massive hematogenous dissemination, chest radiography may reveal the classic diffuse micronodular pattern, although computed tomography (CT) is more sensitive for detecting lesions early (Kwas et al., 2024).

Challenges in Treatment and Adherence

The standard treatment for sensitive TB, whether pulmonary or spinal, requires a multidrug regimen (including isoniazid, rifampicin, pyrazinamide, and ethambutol) for a period of six months (Jaganath et al., 2022; Na et al., 2023). More severe forms, such as miliary TB with central nervous system involvement (tuberculous meningitis) or osteoarticular TB, require prolonged treatments ranging from 9 to 12 months (Jaganath et al., 2022; Kwas et al., 2024).

The main therapeutic challenge, however, lies in the management of latent infection (LTBI). The effectiveness of preventive therapy (PT) has historically been limited by low rates of adherence and completion (Jaganath et al., 2022; Matteelli et al., 2022). Traditional regimens, such as 6 to 9 months of isoniazid (INH) monotherapy, are long and associated with the risk of hepatotoxicity, which decreases adherence in asymptomatic patients (Jaganath et al., 2022; Goletti et al., 2022).

To address low adherence, shorter rifamycin-based regimens have become preferable (Jaganath et al., 2022; Matteelli et al., 2022). Regimens such as 4 months of daily rifampicin (4R) or 3 months of weekly isoniazid and rifapentine (3HP) have demonstrated non-inferiority, greater safety (lower hepatotoxicity), and significantly higher completion rates (Jaganath et al., 2022;

Goletti et al., 2022). Ultra-short regimens, such as 1 month of daily isoniazid and rifapentine (1HP), have also shown promising results in specific populations, such as people living with HIV (Goletti et al., 2022; Matteelli et al., 2022).

In children, administering medication is an additional obstacle. Formulations must be age-appropriate, with dispersible tablets being preferable to liquid solutions, such as isoniazid, which often causes significant gastrointestinal disturbances and is poorly tolerated (Jaganath et al., 2022).

The treatment of tuberculosis in the pediatric population plays a central role in controlling the spread of the disease. Appropriate therapeutic management, especially in cases of active tuberculosis, prevents the emergence of transmissible forms, such as pulmonary tuberculosis. It should be noted that, in most cases, children with latent infection or uncomplicated clinical presentations do not pose a significant risk of transmission (Jaganath et al., 2022).

Early intervention contributes to reducing the bacterial load in the body and, consequently, in the environment, decreasing the likelihood of contagion. Thus, in addition to preventing the progression of the disease and promoting individual protection, timely treatment is an important public health strategy, as it directly contributes to interrupting the chain of transmission (Jaganath et al., 2022).

Finally, the management of drug-resistant TB (DR-TB), particularly multidrug-resistant TB (MDR-TB), requires longer, more complex second-line regimens (involving at least four or five drugs), with greater potential for toxicity and lower efficacy, representing a substantial clinical and public health challenge (Na et al., 2023; Goletti et al., 2022).

CONCLUSION

An integrated analysis of contemporary challenges in the diagnosis and treatment of tuberculosis shows that, despite substantial methodological and therapeutic advances, the disease remains rooted in clinical, biological, and operational determinants that limit the achievement of global elimination goals. The persistence of a large reservoir of latent infection, combined with the inadequacy of current diagnostic methods and prolonged treatment regimens, makes it difficult to accurately differentiate infectious states and adhere to treatment, perpetuating a cycle of silent transmission that compromises more precise and efficient preventive interventions. Therefore, this scenario reinforces the urgency of pharmacological innovation and policies that integrate molecular surveillance, patient support, and more adaptive public health strategies.

In this context, it becomes clear that a successful treatment regimen depends not only on the action of drugs, but also on the ability to offer care that recognizes the complexity of the patient's experience. The duration of regimens, side effects, and the need for constant monitoring highlight how treatment can become exhausting, leading to breaks in treatment and increasing the likelihood of antimicrobial resistance. At the same time, promising alternatives are emerging, such as shorter regimens, combinations of formulations, and intermittent strategies, which have proven effective in reducing dropouts and improving outcomes.

The integration of multidisciplinary practices with rigorous monitoring, psychological support, and education as a fundamental pillar to strengthen the therapeutic bond and increase patient awareness of their participation in the healing process. At the same time, the development of diagnostic tools, especially for vulnerable populations and children, is crucial to guide early treatment initiation and prevent disease progression.

Therefore, progress in the treatment of tuberculosis requires pharmacological innovation and more flexible health policies that can combine molecular surveillance, clinical support, and patient-centered interventions. However, it is through strategies that integrate science, technology, and humanized care that it will be possible to interrupt the cycle of transmission and progress toward a more effective scenario for disease prevention and control.

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