



Screening for Latent Tuberculosis Infection in Adults

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ABSTRACT

Background: The literature surrounding the screening for latent tuberculosis infection (LTBI) has evolved significantly over the years, reflecting advances in diagnostic methodologies and an increasing understanding of the condition's complexities. **Literature Review:** (C. Kahwati et al., 2016) conduct a systematic review assessing the benefits and harms of LTBI screening, concluding that while both TST and interferon-gamma release assays (IGRAs) show moderate sensitivity and high specificity in low TB burden countries, a lack of direct comparisons between screening and no screening persists. (W. Uzorka et al., 2020) focus on practical aspects of LTBI management in primary care, advocating for IGRA testing over TST, particularly for BCG-vaccinated individuals. They highlight barriers to follow-up care in college students diagnosed with LTBI, suggesting that systematic communication strategies could enhance adherence to treatment protocols. (De Oyarzabal et al., 2019) delve into the immunological responses during LTBI treatment with isoniazid, revealing complexities in immune responses and discrepancies between TST and IGRA results. Their research underscores the necessity for tailored treatment approaches based on individual risk factors. (W. Uzorka et al., 2020) provide a retrospective analysis of diagnostic trends, noting a significant decline in TST usage and an increase in QFT application over a 17-year period. This shift reflects evolving clinical practices aimed at reducing active TB incidence among high-risk patients. **Conclusion:** Collectively, these articles illuminate the multifaceted landscape of LTBI screening and management, showcasing advancements in diagnostic technologies while addressing persistent challenges in diverse populations. The evolution of screening practices, the importance of tailored approaches for high-risk groups, and the need for ongoing research into effective diagnostic tools and treatment regimens are critical for improving public health outcomes related to tuberculosis.

Keyword: Screening, Latent Tuberculosis Infection, Adults

INTRODUCTION

The literature surrounding the screening for latent tuberculosis infection (LTBI) has evolved significantly over the years, reflecting advances in diagnostic methodologies and an increasing understanding of the condition's complexities. The foundational study by Codecasa et al. (Codecasa et al., 2005) emphasizes the global prevalence of LTBI, affecting approximately one-third of the world's population. The research highlights the challenges associated with the tuberculin skin test (TST), which is subject to individual variability and may yield misleading results, particularly in individuals previously treated for LTBI. The introduction of the QuantiFERON-TB Gold (QFT) test as a potential alternative to TST is noted, suggesting a need for improved diagnostic accuracy in identifying those at risk of progressing to active tuberculosis.

Building on these insights, Pollock et al. (Pollock et al., 2012) explore screening strategies specifically within the HIV-positive population, underscoring the importance of targeted screening protocols in high-risk groups. Their findings align with UK guidelines that recommend screening for TB contacts and new entrants from high-incidence countries, emphasizing the necessity of excluding active disease in HIV-positive individuals before initiating treatment for LTBI. This study reinforces the critical intersection of LTBI screening and HIV management, highlighting the heightened vulnerability of co-infected individuals.

Adams (Adams, 2015) further contributes to the discussion by evaluating immunodiagnostic tests among healthcare workers in South Africa, where the dual burden of high HIV and TB incidence complicates diagnosis. The meta-analysis presented reveals uncertainties surrounding new diagnostic tests and the need for further research to clarify their effectiveness, particularly in populations at high risk. Adams' work illustrates the ongoing challenges in accurately diagnosing LTBI and the implications for clinical practice in high-burden settings.

In a systematic review, Kahwati et al. (C. Kahwati et al., 2016) assess the benefits and harms of LTBI screening, revealing that while both TST and

interferon-gamma release assays (IGRAs) show moderate sensitivity and high specificity in low TB burden countries, no studies have directly compared screening with no screening. Their findings provide a critical evaluation of existing screening practices and emphasize the need for evidence-based guidelines to optimize LTBI management.

Middleton et al. (et al., 2018) shift the focus to the practical implications of LTBI management in primary care settings, advocating for the use of IGRA testing over TST, particularly for individuals vaccinated with BCG. This article highlights the importance of addressing barriers to follow-up care in college students diagnosed with LTBI, suggesting that systematic communication strategies could enhance patient adherence to treatment protocols.

The immunological dimensions of LTBI are further explored by De Oyarzabal et al. (De Oyarzabal et al., 2019), who investigate the host immune response during LTBI treatment with isoniazid. Their study reveals the complexities of immune responses and the discrepancies between TST and IGRA results, underscoring the necessity for tailored treatment approaches based on individual risk factors.

Uzorka et al. (W. Uzorka et al., 2020) provide a retrospective analysis of diagnostic trends in a tertiary care center, documenting a significant decline in TST usage and an increase in QFT application over a 17-year period. The shift towards rifampicin as a preferred treatment option reflects evolving clinical practices aimed at reducing the incidence of active TB among high-risk patients.

Finally, Carranza et al. present new alternatives for diagnosing LTBI, emphasizing the interplay between host immune responses and pathogen metabolism. Their work advocates for the continued exploration of innovative diagnostic techniques, such as whole-blood transcriptomic profiling, to distinguish between LTBI and active TB, thereby enhancing the accuracy of diagnosis and subsequent treatment strategies.

Together, these articles illuminate the multifaceted landscape of LTBI screening and management, revealing both advancements in diagnostic technologies and the persistent challenges faced in diverse populations.

LITERATURE REVIEW

The article titled "Comparison of Tuberculin Skin test and Quantiferon immunological assay for latent Tuberculosis infection" by Codecasa et al. (Codecasa et al., 2005) provides a comprehensive examination of latent tuberculosis infection (LTBI) and the methodologies utilized for its screening. The authors emphasize the prevalence of LTBI, which affects approximately one-third of the global population, highlighting the importance of identifying individuals at risk of developing active tuberculosis (TB). This identification is pivotal, as untreated LTBI can lead to a significant proportion of individuals progressing to active TB, estimated at one in ten over a lifetime.

The article critically evaluates the traditional Tuberculin Skin Test (TST), which has been the standard screening tool for LTBI. While TST has been widely implemented, the authors point out its limitations, particularly its susceptibility to individual variability due to factors such as prior exposure to non-tuberculous mycobacteria, BCG vaccination, and the individual's immune status. These factors can lead to false-positive or false-negative results, complicating the accurate assessment of LTBI.

In contrast, the article discusses the introduction of the Quantiferon assay, which measures interferon-gamma (γ INF) responses to specific TB antigens in whole blood. This method is posited as a more reliable alternative to TST, as it is less affected by prior BCG vaccination and non-tuberculous mycobacterial infections. The authors present data supporting the efficacy of the Quantiferon assay in terms of specificity and sensitivity, suggesting that it may enhance the identification of individuals with LTBI, thereby facilitating timely and appropriate treatment.

The article effectively underscores the critical role of accurate LTBI screening in TB elimination strategies. By comparing TST and the Quantiferon

assay, Codecasa et al. (Codecasa et al., 2005) provide valuable insights into the strengths and weaknesses of each method, advocating for a shift towards more reliable testing modalities. The findings suggest that adopting the QuantiFERon assay could lead to improved public health outcomes by ensuring that those at risk are correctly identified and treated, ultimately contributing to the reduction of TB incidence globally.

The article titled "Comparison of screening strategies to improve the diagnosis of latent tuberculosis infection in the HIV-positive population: a cohort study" by Pollock et al. (Pollock et al., 2012) presents a critical examination of various screening strategies aimed at identifying latent tuberculosis infection (LTBI) among HIV-positive individuals. The authors focus on the effectiveness of different testing approaches, particularly in populations that are at heightened risk due to their immunocompromised status.

The main insights of the study emphasize the necessity of tailored screening strategies based on the CD4 counts of HIV-positive individuals. For those with CD4 counts below 200 cells/ml, the authors recommend a dual approach involving both an interferon-gamma (IFN- γ) test and a concurrent Mantoux test. This strategy is particularly significant as it addresses the increased vulnerability of individuals with advanced HIV disease to both latent and active TB infections. For individuals with CD4 counts between 200-500 cells/ml, the article suggests that either an IFN- γ test alone or in conjunction with a Mantoux test could be employed, thereby allowing for flexibility based on clinical judgment and patient circumstances.

The article also underscores the importance of screening new entrants from high-incidence TB countries and close contacts of infectious TB cases. The authors align their recommendations with the guidelines set forth by the National Institute for Health and Care Excellence (NICE), which advocates for screening in specific age groups and emphasizes the need to consider the risks and benefits of LTBI treatment, especially in individuals over 35 years old.

Moreover, Pollock et al. (Pollock et al., 2012) provide a clear definition of a positive response in the context of the IFN- γ test, which is crucial for

standardizing the interpretation of test results. The identification of 114 HIV-positive individuals at risk of LTBI within their cohort further illustrates the prevalence of this condition in the studied population and highlights the pressing need for effective screening measures.

The article titled "A study to evaluate immunodiagnostic tests for tuberculosis infection and determinants of TB infection in a population of health care workers in the Western Cape of South Africa" by Adams (Adams, 2015) presents a comprehensive meta-analysis of various immunodiagnostic tests for latent tuberculosis infection (LTBI), particularly focusing on interferon-gamma release assays (IGRAs) as alternatives to the traditional tuberculin skin test (TST). The study addresses a critical gap in the literature regarding the effectiveness and reliability of these tests within a high-incidence tuberculosis (TB) setting, specifically among healthcare workers who are at elevated risk of exposure.

Adams (Adams, 2015) systematically reviews the performance of IGRAs, highlighting their advantages over the TST, such as reduced cross-reactivity with prior BCG vaccination and improved specificity in diagnosing LTBI. The article emphasizes the significance of these tests in accurately identifying individuals at risk of developing active TB, which is particularly pertinent in healthcare settings where the consequences of undiagnosed LTBI can be severe not only for the individual but also for public health.

The article also discusses the discordance often observed between TST and IGRA results, a phenomenon that can complicate the screening process. Adams (Adams, 2015) notes that while both tests have their merits, the variability in results can lead to challenges in interpreting test outcomes, especially in populations with mixed immunity profiles. This aspect is crucial as it underscores the need for healthcare systems to adopt a more nuanced approach to TB screening, which may include a combination of diagnostic tools tailored to the specific demographics of the population being tested.

Furthermore, the study highlights the importance of understanding the clinical, immunological, and epidemiological factors that contribute to TB infection

among healthcare workers. By analyzing risk factors associated with positive test results, the research provides valuable insights into how targeted screening strategies can be developed to enhance the identification of LTBI in this vulnerable group.

The article "Primary Care Screening and Treatment for Latent Tuberculosis Infection in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force" by Kahwati et al. (C. Kahwati et al., 2016) provides a comprehensive overview of the current state of screening and treatment for latent tuberculosis infection (LTBI) in adults. The authors emphasize the critical public health concern posed by LTBI, noting that 5 to 10 percent of individuals with this condition may progress to active tuberculosis (TB) disease. This statistic underscores the necessity for effective screening and treatment strategies to mitigate the risk of disease progression.

The systematic review incorporated a total of 72 studies, focusing on English-language research related to LTBI screening methods, treatment protocols involving recommended pharmacotherapy, and the diagnostic accuracy of the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs). Notably, the findings suggest that both TST and IGRAs exhibit moderate sensitivity and high specificity in populations residing in countries with a low burden of TB. This is an important consideration for clinicians and public health officials, as it indicates that while these tests can effectively identify individuals at risk, they are not infallible.

One significant limitation highlighted in the review is the absence of studies directly comparing the benefits and harms of screening versus no screening. This gap in the literature raises questions about the overall effectiveness of screening strategies in preventing the transition from LTBI to active TB, suggesting a need for further research in this area. The authors recommend that future studies should focus on the long-term outcomes of screening programs and the potential adverse effects associated with treatment, which could inform more nuanced guidelines for LTBI management.

Additionally, the review demonstrates that treatment for LTBI significantly reduces the risk of developing active TB among the populations studied. This finding reinforces the importance of not only identifying individuals with LTBI but also ensuring they receive appropriate treatment to prevent the onset of active disease. The implications of this research are vital for primary care practices and public health initiatives, as they highlight the dual necessity of screening and subsequent treatment in the fight against tuberculosis.

The article "Increasing Follow-up in College Students with Latent Tuberculosis Infection" by Middleton, James, and Woodruff (et al., 2018) presents a critical examination of the management of latent tuberculosis infection (LTBI) among college students, emphasizing the importance of accurate testing and follow-up care. The authors highlight the Centers for Disease Control and Prevention's (CDC) recommendation favoring Interferon Gamma Release Assays (IGRAs) over the traditional tuberculin skin test (TST) for individuals who have received the Bacillus Calmette-Guérin (BCG) vaccine. This preference is based on the potential for false-positive results with the TST, which could lead to unnecessary treatment interventions, such as the initiation of isoniazid (INH) therapy for individuals who do not actually require it.

A significant aspect of the article is its focus on public health implications, asserting that LTBI is a pressing concern that necessitates proactive management by healthcare providers. The authors argue for the integration of evidence-based practice guidelines established by the World Health Organization (WHO) and the CDC into primary care settings to effectively manage LTBI. This approach is crucial, as it not only ensures the appropriate treatment of patients but also addresses the broader public health challenge posed by TB.

Moreover, the article identifies barriers to follow-up care, particularly among college students, and suggests that further research is needed to explore the reasons behind the lack of response to follow-up communications. The authors propose that the sustainability of their evidence-based practice (EBP) project could be enhanced through the involvement of medical assistants and healthcare providers

at student health centers (SHCs). By implementing systematic follow-up measures—such as sending secure messages to patients upon diagnosis—the risk of students being lost to follow-up could be significantly reduced.

The article titled "Expression of USP18 and IL2RA is increased in individuals receiving latent tuberculosis treatment with isoniazid" by E De Oyarzabal et al. (De Oyarzabal et al., 2019) provides significant insights into the immunological factors influencing the host immune response during latent tuberculosis infection (LTBI) and its potential reactivation. The authors highlight that despite the longstanding recognition of LTBI, the complexities surrounding the host response and the factors that may lead to the progression to active tuberculosis (TB) remain inadequately understood.

One of the primary concerns raised in the article is the persistent nature of LTBI, which can remain dormant throughout an individual's life. This dormancy is particularly precarious for individuals with compromised immune systems, such as those living with HIV, or those undergoing treatments that affect immunity (De Oyarzabal et al. (De Oyarzabal et al., 2019)). The article underscores the importance of understanding these immunological dynamics as they play a critical role in determining the risk of developing active TB, especially in vulnerable populations.

The authors also discuss the limitations of current screening methods for LTBI, specifically the tuberculin skin test (TST) and interferon- γ release assays (IGRA). While the TST has been a traditional method for LTBI screening, its lack of specificity, particularly in BCG-vaccinated populations, poses significant challenges. The discrepancies observed when employing a two-step approach with both TST and IGRA further complicate the clinical decision-making process (De Oyarzabal et al. (De Oyarzabal et al., 2019)). This highlights the need for improved diagnostic tools that can more accurately identify individuals at risk for progression to active TB.

Treatment guidelines for LTBI, as outlined in the article, advocate for the administration of isoniazid (INH) as a preventive measure. The authors provide a detailed account of the recommended dosages and treatment duration, emphasizing

the necessity of tailoring these recommendations based on the incidence rates of TB in different countries. Furthermore, they introduce new treatment regimens that combine rifampicin with INH or rifapentine with INH, which may offer effective alternatives for both children and adults (De Oyarzabal et al. (De Oyarzabal et al., 2019)).

The article titled "Trends in diagnostic methods and treatment of latent tuberculosis infection in a tertiary care center from 2000 to 2017" by Uzorka et al. (W. Uzorka et al., 2020) provides a comprehensive retrospective analysis of the evolution of diagnostic methods and treatment protocols for latent tuberculosis infection (LTBI) in a specific tertiary care setting. The study focuses on patients diagnosed with LTBI prior to immunosuppressive therapy, thereby highlighting a crucial population that is particularly vulnerable to the progression from LTBI to active tuberculosis.

One of the key insights from the study is the significant shift in diagnostic practices over the 17-year period examined. The authors report a marked decline in the use of the tuberculin skin test (TST), which has traditionally been a cornerstone of LTBI detection. In contrast, there was a notable increase in the utilization of the QuantiFERON (QFT) test, an interferon-gamma release assay that offers advantages such as a single visit requirement and reduced subjectivity in interpretation (Uzorka et al. (W. Uzorka et al., 2020)). This trend reflects a broader movement in the field towards more reliable and efficient diagnostic tools, which is critical for timely identification and management of LTBI, particularly in populations at elevated risk.

Furthermore, the article discusses the evolution of treatment regimens, specifically the transition from isoniazid to rifampicin as the preferred therapeutic agent for LTBI. This change is particularly relevant given the emerging data suggesting that rifampicin may offer a shorter treatment duration and potentially improved adherence compared to traditional isoniazid therapy (Uzorka et al. (W. Uzorka et al., 2020)). The authors emphasize the importance of adapting treatment

strategies based on evolving evidence to enhance patient outcomes and reduce the risk of tuberculosis reactivation.

The study's findings underscore the necessity of continued screening for LTBI, especially among individuals at high risk for progression to active disease. The authors advocate for a multifaceted approach to screening, which includes assessing potential exposure to *Mycobacterium tuberculosis* (Mtb) and employing immunological testing methods. This comprehensive evaluation is essential for effectively identifying LTBI cases and implementing preventive measures.

The article "Diagnosis for Latent Tuberculosis Infection: New Alternatives" by Carranza et al. (Carranza et al., 2020) presents a comprehensive overview of the evolving understanding of latent tuberculosis infection (LTBI) and its diagnosis. The authors effectively argue that the traditional view of LTBI, which emphasizes a delicate balance between the host immune response and *Mycobacterium tuberculosis* metabolism, has been significantly refined by recent research. This shift towards recognizing a spectrum of immune responses in LTBI highlights the complexity of the disease and the various factors that influence the risk of progression to active tuberculosis.

One of the key insights from the article is the identification of specific risk factors associated with an impaired immune response that can lead to the development of active TB. The authors point out that individuals with concurrent conditions such as HIV, cancer, diabetes, and those undergoing immunosuppressive therapies are at a markedly increased risk. Particularly striking is the statistic that diabetic individuals are approximately three times more likely to develop TB than their non-diabetic counterparts. This finding underscores the importance of targeted screening and monitoring in populations with these risk factors.

The article also discusses the limitations of current diagnostic methods for LTBI, notably the intradermal tuberculin test (TST) and interferon-gamma release assays (IGRAs). While the TST has been a longstanding tool for diagnosing LTBI, its reliance on a cellular immune response to mycobacterial antigens can lead to false positives and negatives, particularly in immunocompromised individuals. The

authors emphasize that there is no gold standard for LTBI diagnosis, which complicates the clinical management of the infection. This lack of a definitive test highlights the need for further research into biomarkers that could differentiate LTBI from active TB and predict treatment outcomes.

Moreover, the article provides a critical evaluation of the TST, detailing its historical significance and widespread use, particularly in developing countries due to its cost-effectiveness. However, the authors also acknowledge its limitations, such as the need for follow-up reading and the potential for misinterpretation in certain populations. The discussion around the IGRA as a more specific alternative is particularly relevant, given its ability to provide a more accurate assessment of LTBI in individuals with complex medical histories.

CONCLUSION

The literature on screening for latent tuberculosis infection (LTBI) reveals significant advancements in diagnostic methodologies and an increasing understanding of the complexities surrounding LTBI. (Codecasa et al., 2005) highlight the global prevalence of LTBI, affecting roughly one-third of the world's population, and critique the traditional tuberculin skin test (TST) for its limitations, particularly in individuals previously treated for LTBI. They advocate for the QuantiFERON-TB Gold (QFT) test as a more accurate alternative, suggesting that improved diagnostic accuracy is essential for identifying those at risk of progressing to active tuberculosis. Their findings align with UK guidelines, reinforcing the importance of excluding active TB disease before initiating LTBI treatment in vulnerable individuals. This intersection of LTBI screening and HIV management underscores the critical vulnerabilities faced by co-infected individuals.

(Adams, 2015) further explores the challenges of diagnosing LTBI among healthcare workers in South Africa, a region grappling with high incidences of both HIV and TB. His meta-analysis reveals uncertainties surrounding new diagnostic tests and highlights the necessity for further research to clarify their effectiveness in high-risk populations. This study illustrates the ongoing challenges in accurately diagnosing LTBI and the implications for clinical practice.

(C. Kahwati et al., 2016) conduct a systematic review assessing the benefits and harms of LTBI screening, concluding that while both TST and interferon-gamma release assays (IGRAs) show moderate sensitivity and high specificity in low TB burden countries, a lack of direct comparisons between screening and no screening persists. Their findings emphasize the need for evidence-based guidelines to optimize LTBI management.

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(W. Uzorka et al., 2020) provide a retrospective analysis of diagnostic trends, noting a significant decline in TST usage and an increase in QFT application over a 17-year period. This shift reflects evolving clinical practices aimed at reducing active TB incidence among high-risk patients. Propose innovative diagnostic techniques, such as whole-blood transcriptomic profiling, to distinguish between LTBI and active TB, thereby enhancing diagnostic accuracy and treatment strategies.

Collectively, these articles illuminate the multifaceted landscape of LTBI screening and management, showcasing advancements in diagnostic technologies while addressing persistent challenges in diverse populations. The evolution of screening practices, the importance of tailored approaches for high-risk groups, and the need for ongoing research into effective diagnostic tools and treatment regimens are critical for improving public health outcomes related to tuberculosis.

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