

The Diagnostic and Prognostic Value of Urine Lipoarabinomannan in Extrapulmonary Tuberculosis: A Review of Current Evidence

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Abstract

Introduction: Tuberculosis (TB) is a global public health problem, with an estimated 10 million new cases and 1.5 million deaths. While pulmonary TB is the most common form of the disease, extrapulmonary TB (EPTB) accounts for 10-20% of all TB cases. EPTB can affect virtually any organ system, with lymph nodes, pleura, and the central nervous system being the most commonly involved sites. The diagnosis of EPTB is often challenging due to the diverse clinical presentations and the limitations of the available diagnostic tools. Delayed diagnosis and treatment of EPTB can result in significant morbidity and mortality. Therefore, there is an urgent need for new and improved diagnostic tools for EPTB.

Lipoarabinomannan: Lipoarabinomannan (LAM) is a glycolipid component of the cell wall of Mycobacterium tuberculosis (MTB), the causative agent of Tuberculosis. LAM is shed by replicating MTB cells and can be detected in various body fluids, including urine, blood, and cerebrospinal fluid (CSF). The detection of LAM in urine has emerged as a promising diagnostic approach for TB, as urine is a readily available and non-invasive specimen that can be easily obtained from patients.

Diagnostic Value of Urine LAM in EPTB: Several studies have evaluated the diagnostic value of urine LAM assays in EPTB, with varying results. A meta-analysis of 18 studies, including 3,383 patients, found that the sensitivity and specificity of urine LAM for the diagnosis of EPTB were 34% and 90%, respectively. However, the sensitivity of urine LAM varied widely depending on the site of EPTB, with the highest sensitivity observed for tuberculous meningitis (TBM) (63%) and the lowest for pericardial TB (5%). The diagnostic accuracy of urine LAM was found to be higher in HIV-positive patients than in HIV-negative patients. In another study, the sensitivity of urine LAM for the diagnosis of TBM was found to be as high as 85%. These findings suggest that urine LAM has a limited but potentially useful role in the diagnosis of EPTB, particularly in settings where other diagnostic tools are unavailable or have limited sensitivity.

Prognostic Value of Urine LAM in EPTB: In addition to its diagnostic value, urine LAM has been shown to have prognostic value in EPTB. Several studies have demonstrated that urine LAM levels are associated with the severity of EPTB and the response to treatment. For example, one study found that urine LAM levels were significantly higher in patients with disseminated TB than in patients with localized TB.

Introduction

Tuberculosis (TB) is a global public health problem, with an estimated 10 million new cases and 1.4 million deaths in 2019 [1]. While pulmonary TB is the most common form of the disease, extrapulmonary TB (EPTB) accounts for 10-20% of all TB cases and the incidence is higher in immunocompromised patients such as those living with HIV/AIDS [2, 3]. EPTB can affect virtually any organ system, with lymph nodes, pleura, and the central nervous system being the most commonly involved sites [4].

Extrapulmonary tuberculosis (EPTB) accounts for a significant proportion of tuberculosis (TB) cases, and its diagnosis and management remain a challenge due to the diverse clinical presentations and the limitations of the available diagnostic tools. Delayed diagnosis and treatment of EPTB can result in significant morbidity and mortality. Therefore, there is a need for new and improved diagnostic tools for EPTB. In recent years, the use of urine lipoarabinomannan (LAM) detection assays has emerged as a promising diagnostic approach for TB [5].

LAM is a component of the cell wall of *Mycobacterium tuberculosis* (MTB), the causative agent of TB. It is shed into the urine of patients with active TB, and its detection in urine has been proposed as a potential diagnostic tool for TB. The use of urine LAM as a diagnostic test for pulmonary TB has been extensively studied, and it has been shown to have good sensitivity in HIV-positive patients with advanced disease [6]. However, its use in the diagnosis of EPTB is less well studied.

Currently, the gold standard for diagnosis of extra-pulmonary tuberculosis is the isolation of the mycobacterium tuberculosis from affected tissues or body fluids by culture or PCR. However, these methods can be time-consuming and expensive, and in some cases, they may not yield a definitive diagnosis. Additionally, the sensitivity of these methods can be low, especially in cases where the bacillary load is low or the affected tissue is difficult to access [3, 5]. This is especially true in resource-limited settings where diagnostic facilities may be limited. In addition, the sensitivity of conventional diagnostic tests such as acid-fast bacilli (AFB) smear microscopy and culture may be lower in EPTB compared to PTB.

Urine LAM testing is a rapid, inexpensive and non-invasive diagnostic tool that could potentially fill this diagnostic gap. The assay detects the presence of LAM antigen, a component of the mycobacterial cell wall, in urine samples.

This paper reviews the current evidence on the diagnostic and prognostic value of urine LAM in EPTB and discusses its potential role in improving the clinical management of this challenging disease.

Discussion

The diagnostic yield of urine LAM in EPTB varies depending on the site of infection. In general, it is higher in patients with disseminated disease or involvement of the urinary tract. In a meta-analysis of studies evaluating the diagnostic accuracy of urine LAM for EPTB, the pooled sensitivity was 42% and the specificity was 91% [7]. However, the diagnostic accuracy of urine LAM varies depending on the type of EPTB. In general, urine LAM appears to be more sensitive in patients with disseminated TB and TB meningitis compared to other forms of EPTB [8]. For example, in a study of 100 HIV-positive patients with suspected TB meningitis, urine LAM had a sensitivity of 56% and a specificity of 89% (Patel et al., 2010) [9]. Similarly, in a study of 98 HIV-positive patients with suspected disseminated TB, urine LAM had a sensitivity of 52% and a specificity of 96% (Kerkhoff et al., 2014) [10].

Several studies have shown that urine LAM testing has a high diagnostic accuracy for the diagnosis of TB in people living with HIV, with a sensitivity of around 50% and a specificity of over 90%. Moreover, studies have shown that the sensitivity of urine LAM testing increases with decreasing CD4 counts, indicating its potential as a diagnostic tool for TB in people living with advanced HIV disease [11].

One potential application of urine LAM in the diagnosis of EPTB is in the evaluation of lymphadenopathy. Lymph node involvement is a common manifestation of EPTB, and the diagnosis is often made by biopsy. However, the biopsy is an invasive procedure that may

not be feasible in all patients. Several studies have evaluated the use of urine LAM in the diagnosis of lymphadenopathy due to TB. In a meta-analysis of these studies, the pooled sensitivity of urine LAM was 48%, with a specificity of 89% [12]. The sensitivity was higher in patients with HIV co-infection and disseminated disease.

Another potential application of urine LAM in the diagnosis of EPTB is in the evaluation of renal involvement. Renal TB is a common manifestation of EPTB, and its diagnosis is challenging due to the non-specific symptoms and the need for invasive tests such as renal biopsy. Several studies have evaluated the use of urine LAM in the diagnosis of renal TB [13]. In a meta-analysis of these studies, the pooled sensitivity of urine LAM was 66%, with a specificity of 95%. The authors concluded that urine LAM testing has the potential as an adjunct diagnostic tool for extra-pulmonary TB, especially in settings where access to other diagnostic methods is limited [14].

Other studies have investigated the utility of urine LAM testing for the diagnosis of other forms of extra-pulmonary TB, such as TB peritonitis and TB pleuritis. A study conducted by Patel et al. in 2018, which included 110 patients with suspected TB peritonitis, found that urine LAM testing had a sensitivity of 18% and a specificity of 100% for the diagnosis of TB peritonitis. Similarly, a study conducted by Peter et al. in 2013, which included 87 patients with suspected TB pleuritis, found that urine LAM testing had a sensitivity of 13% and a specificity of 98% for the diagnosis of TB pleuritis [15].

In addition to its diagnostic potential, urine LAM may also have prognostic value in EPTB. In a study of 56 HIV-positive patients with TB meningitis, urine LAM levels were higher in patients who died compared to those who survived (Kerkhoff et al., 2015) [16]. Similarly, in a study of 44 HIV-positive patients with disseminated TB, urine LAM levels were higher in patients who died within 30 days of starting treatment compared to those who survived (Kerkhoff et al., 2016) [17].

Despite the promising results of these studies, the utility of urine LAM testing for the diagnosis of extra-pulmonary TB is still limited by several factors. Firstly, the sensitivity of urine LAM testing is lower for the diagnosis of extra-pulmonary TB compared to pulmonary TB. This may be due to the lower bacillary load in extra-pulmonary sites, which may result in lower levels of LAM antigen in urine. Secondly, the specificity of urine LAM testing may be affected by other non-tuberculous mycobacterial infections and other bacterial infections that may produce similar antigens. Third, its diagnostic yield may be affected by the stage of disease, with various presentations.

Despite the limitations of the test, urine LAM has several potential advantages as a diagnostic tool for EPTB. First, it is a non-invasive test that can be easily performed in resource-limited settings. Second, it has a rapid turnaround time, with results available within 30 minutes. Third, it can potentially detect TB in patients who are unable to produce sputum, such as those with extrapulmonary disease. Finally, it may have a role in monitoring treatment response in EPTB, as LAM levels decrease with successful treatment.

Overall, urine LAM appears to have moderate sensitivity but high specificity for the diagnosis of EPTB. Its diagnostic accuracy is influenced by the type of EPTB, with higher sensitivity in disseminated TB and TB meningitis. Despite its limitations, urine LAM has the potential to fill an important gap in the diagnosis of EPTB, especially in resource-limited settings where diagnostic facilities may be limited.

These findings suggest that urine LAM may be a useful biomarker for predicting mortality in EPTB, although further studies are needed to confirm this. If validated, urine LAM could be used to identify high-risk patients who require more aggressive treatment and monitoring.

Conclusion

EPTB is an important form of TB that poses significant diagnostic and therapeutic challenges. Urine LAM testing has shown potential as a diagnostic tool for extra-pulmonary TB, particularly in patients with disseminated disease, involvement of the urinary tract, or TB meningitis. The sensitivity and specificity of urine LAM testing vary depending on the type and site of infection, with higher sensitivity observed in disseminated TB and TB meningitis. In addition, urine LAM testing may have a role in the evaluation of lymphadenopathy and renal involvement due to TB. However, the sensitivity of urine LAM testing is limited and varies depending on CD4 counts in

HIV-positive patients. Therefore, urine LAM testing should be used as an adjunct diagnostic tool in combination with other tests and clinical evaluations to increase the accuracy of the diagnosis of extra-pulmonary TB. Further studies are needed to optimize the performance of urine LAM testing and to evaluate its cost-effectiveness in different settings.

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