Clinical, radiological and laboratory predictors of a positive urine lipoarabinomannan in sputum scarce and sputum negative patients with HIV associated TB in two Johannesburg hospitals

Lior Chernick[1 3], Ismail S Kalla[1 2], Michelle Venter[1 3]

[1]University of the Witwatersrand, [2]Charlotte Maxeke Johannesburg Academic Hospital, [3]Chris Hani Baragwanath Academic Hospital

Background

- South Africa has the one of the highest global incidences of tuberculosis (TB), the majority whom are HIV positive[1].
- In resource limited settings such as SA, up to 48% of patients coinfected with advanced HIV and TB, are undiagnosed ante-mortem[2].
- The accurate diagnosis of TB in people living with HIV (PLWH) is made difficult by the atypical and often nonspecific presentation of disease especially in those with advanced disease (CD4<200)[3].
- Patients in this population may be either *sputum negative* due to paucibacillary disease[3] or *sputum scarce* (unable to produce sputum)[4] do to extrapulmonary TB or severe illness limiting the utility of sputum-based diagnostics.
- Disseminated TB (TB in two or more non-contiguous sites, MTB recovered from blood or bone marrow, or miliary TB[5]) is common in this population[6] and diagnosis is often delayed resulting in high mortality.
- The Alere (Abott) Determine™ TB LAM, is a point of care lateral flow based assay (*figure 1*) that detects a form of lipoarabinomannan (LAM), a glycolipid component of the mycobacterial cell wall.
- It has been recommended by the WHO for PLWH with a CD4 < 200 or seriously ill [7] but is not uniformly available at public sector hospitals in SA.
- The relatively poor sensitivity and limited recommendations contribute towards the under-appreciation and underuse of urine LAM as a diagnostic tool.

Objectives & Methods

- The **objective** of the study was to define the clinical, laboratory and radiological associations of TB as detected with urine LAM testing of hospitalised PLWH that were *sputum scarce* or *negative* to improve its diagnostic yield
- This was a multicentre retrospective record-review of adult patients admitted in 201 to the Helen Joseph Hospital and Charlotte Maxeke Academic Hospital in Johannesburg, South Africa.
- The study population consisted of hospitalized PLWH with a CD4 count <100 cells/µL, or seriously ill by previously defined criteria[7] regardless of the CD4 count who, were sputum scarce or sputum negative using Xpert™ MTB/RIF or sputum culture.
- Each had a LAM (Alere Determine™ TB LAM Ag) test performed on a random urine sample for suspected TB during their admission.

Results

- A total of 342 patients were included in the study, one third (n = 121, 35%) had a positive urine LAM.
- Of the 168 patients diagnosed with TB in the study population, a urine LAM was the only microbiological confirmatory modality of TB in half, n=87 (52%).
- The yield (and sensitivity) of urine LAM testing was inversely proportional to CD4 count
- Clinical features with a positive predictive value for a positive urine LAM included patients with drenching night sweats & weight loss, reduced mobility, confusion, a lower median BP and a higher median HR, suggesting an overall sicker patient group.
- A qSOFA score showed a significant correlation with proportional increases in LAM yield relative to a higher score for a given patient.
- There was a significant association of urine LAM with more disseminated forms of TB (OR 13).
- In patients with a diagnosis of TB-IRIS, 88% had a positive LAM test (OR 13.5).
- Similar to the findings of Nel *et al*[7], *in* this study, 75% (n = 9) of confirmed disseminated NTM infections had a positive urine LAM.
- LAM was useful in the interpretation of abdominal sonographic features of tuberculosis (splenic micro-abscesses, lymphadenopathy) which in isolation lack sensitivity/specificity [8]
- A positive urine LAM was associated with severe anaemia (OR=2), abnormal GFR and a CRP of >100mg/L (OR=1.9).

Table 1 - TB Parameters	N	LAM + (n = 121) n (%)	LAM - (n = 221) n (%)	*p* value	OR (95% CI)
Sputum results, n (%)					
Sputum scarce	156	66 (42)	90 (58)	0.0141*	1.7 (1.3-2.7)
Sputum negative	186	55 (30)	131 (70)		
TB diagnosis (all sites), n (%)	168	121 (72)	47 (28)		
Microbiology (PCR/Culture) positive	48	34 (71)	14 (29)	0.8279	0.9 (0.4-1.9)
Microbiology (PCR/Culture) negative	120	87 (73)	33 (27)		
LAM sole diagnostic modality¶	87 (52)				
Site involved, n (%)					
Disseminated disease§	52	43 (83)	9 (17)	<0,0001*	13.0 (6.0-27.8)
Miliary†	10	7 (70)	3 (30)	0,0376*	4.5 (1.2-16.1)
Bone Marrow	7	7 (100)	0 (0)	0,0006*	∞ (3.4-∞)
Mycobacteraemia	33	27 (82)	6 (18)	<0,0001*	8.4 (3.3-20.3)
Median time to positivity, days (IQR)		21 (16-28)	22 (15-27)	0.7759	
Pulmonary†	28	22 (79)	6 (21)	<0,0001*	8.0 (3.1-19.2)
Abdominal,	55	40 (73)	15 (27)	<0,0001*	6.8 (3.5-12.5)
Lymph node	10	6 (60)	4 (40)	0.1753	2.8 (0.7-9.0)
CNS	18	7 (39)	11 (61)	0.7491	1.7 (0.5-3.1)
Pleural	5	1 (20)	4 (80)	0.6597	0.5 (0.0-2.8)
IRIS	8	7 (88)	1 (12)	0,0035*	13.5 (2.2 - 152.8)
NTM‡ (disseminated)	12	9 (75)	3 (25)	0.0053*	5.8 (1.6-20.3)

* Statistically significant

¶ Of those with final TB diagnosis, urine LAM was the only microbiological diagnostic method found to be positive

§ TB in two or more sites, blood or bone marrow culture, or radiological evidence of miliary TB

† Diagnosis based on suggestive chest radiography

‡ Non-tuberculous mycobacteria

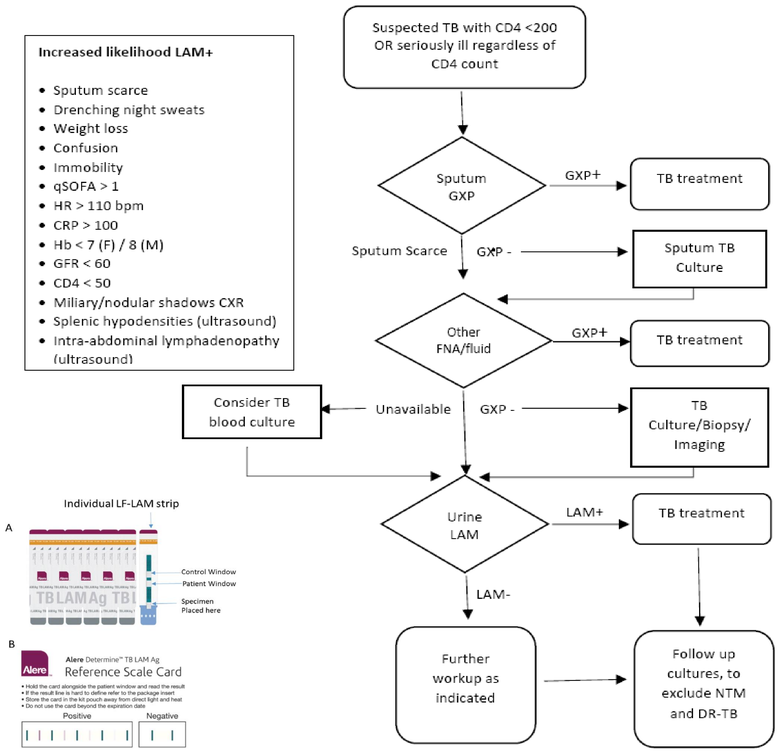

Figure 2 – Suggested algorithm for urine LAM testing with factors increasing likelihood of positive result

Figure 1 – Alere / Abott Determine™ TB LAM (with permission from Abott laboratories)

Table 2 - Laboratory markers	N	LAM + n (%)	LAM - n (%)	*p value*	OR (95% CI)
WCC (×10⁹ cells/L)	339#	119	221		
Median (IQR)		6 (3.9-9.1)	5.1 (3.2-8)	0.1263	
Hb (g/dL)	341#	120	221		
Median (IQR)		9.1 (7-11)	10.6 (8.5-12)	<0,0001*	
Severe anaemia†		30 (25)	31 (14)	0.0116*	2 (1.2-3.5)
GFR (mL/min/1.73m²)	340#	119	221		
Median (IQR)		73 (44-103)	85 (56-109)	0.068	
< 60		49 (41)	67 (30)	0.044*	1.6 (1-2.5)
CRP (mg/L)	317#	115	202		
Median (IQR)		125 (54-200)	91 (23-157)	0.0131*	
>100		72 (63)	94 (47)	0.0059*	1.9 (1.2-3.1)
CD4 count					
Available data	326#	115 (35)	211 (65)		
Median, cells/µL (IQR)		22 (7-42)	26 (10-55)	0.0944	
< 50 cells/µL		92 (80)	147 (70)	0.0439*	1.7* (1.01-3.0)
Urinalysis					
Available data	103#	47	56		
Sterile pyuria§		15 (32)	20 (36)	0.6851	0.8 (0.4-1.8)
Available data	59#	31	28		
Urine PCR > 3.5g/µmol		8 (26)	2 (7)	0.0838	4.5 (0.9-22.4)

WCC, white cell count; Hb, haemaglobin; GFR, glomerular filtration rate; CRP, C-reative protein

* Statistically significant

Number of records with relevant data available

† Hb < 8g/dL for males and <7g/dL for females

§ >10000 cells/µL in the absence of bacterial culture

Conclusions

- Urine LAM is a simple POC test and takes only 25 minutes to establish a result and can be incorporated into a diagnostic algorithm for TB (*figure 2*).
- It was useful in hospitalised PLWH with CD4 counts of less than 100 cells/µL or in the seriously ill, who were *sputum scarce* or *sputum negative*, with a higher yield in the former.
- A positive LAM result predicted a seriously ill subset of patients known to be at significant risk of mortality[10], and was associated with disseminated and EPTB for whom diagnosis in resource limited settings is often difficult or delayed.
- It was helpful in establishing the diagnosis of a TB IRIS where suspected.
- Associations with positive LAM included severe anaemia, renal dysfunction, and an increased yield in those patients who were immobile or confused.
- False positive results may be encountered in patients with disseminated NTM infections.
- The urine LAM test is a definite advance in the early confirmation of life-threatening infection with MTB in PLWH with advanced immunosuppression.

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