Performance of (1,3)-β- D-Glucan in Bronchoalveolar Lavage of Lung Transplant Recipients for the Diagnosis of Invasive Aspergillosis

Archana Bhaskaran, Lianne Singer, Tony Mazzulli, Taisa Prochnow, Coleman Rotstein and Shahid Husain

University Health Network, University of Toronto, Toronto, Canada

archana.bhaskaran@uhn.ca

Abstract

The role of (1, 3)-β-d-glucan **(BDG)** in bronchoalveolar lavage **(BAL)** is not well characterized. We studied the performance of the antigen in BAL of lung transplant recipients **(LTRs)**. One hundred and forty four available BAL samples in 74 LTRs were included. There were 3 episodes of invasive pulmonary aspergillosis **(IPA)** and 55 respiratory fungal colonizations. At a cut-off of 107 pg/ml, the sensitivity and specificity of the test for IPA was 67% and 64% respectively. The median BAL BDG values were not elevated in respiratory fungal colonization. Further studies with higher numbers of invasive pulmonary aspergillosis are warranted.

Background

(1, 3)-β-d-glucan is a constituent of the cell wall of yeast and mold except Cryptococcus and Zygomycetes. This antigen has been well studied in serum for the diagnosis of invasive fungal infection in hematological malignancy and hematopoietic stem cell transplant patients. In this patient population a single serum BDG carries a sensitivity and specificity of 57% and 97% for invasive aspergillosis and 73% and 97% for invasive candidiasis respectively[1].

However serum BDG did not perform very well in lung transplant patients[2]. BDG in bronchoalveolar lavage fluid for the diagnosis of invasive fungal infection has not been well studied. There is no report of BAL BDG performance in lung transplant recipients. Lung transplant patients are prone to pulmonary invasive aspergillosis and tracheobronchitis from *Aspergillus spp.*

Objectives

To determine the performance of BDG in BAL of lung transplant recipients for the diagnosis of invasive pulmonary aspergillosis.

Methods

• One hundred and forty four available BAL samples in 74 lung transplant recipients were included for the study.

• The following information was collected from the electronic medical record: Name, age, sex, date of transplant, reason for transplant, CMV serostatus, indication for bronchoscopy, bronchoscopic findings, microbiologic data in BAL including galactomannan **(GM)**, histopathology, imaging findings and anti-fungal therapy.

• With the above information a fungal diagnosis was ascertained for each episode using ISHLT criteria[3]. BAL samples were processed for BDG using the commercially available Fungitell assay (Associates of Cape Cod Inc, Falmouth, MA, USA).

Statistics

• Median and interquartile range of beta-d-glucan values were determined for the different fungal diagnostic categories.

• The generalized estimating equations regression was used to construct the receiver operator characteristic (ROC) curve to derive the optimum cut-off for sensitivity and specificity.

Results

• Demographics of the 74 patients are displayed in Table 1.

• The 144 events were categorized into mutually exclusive groups: 3 with probable invasive pulmonary aspergillosis, 9 *Aspergillus spp*. colonization, 14 mold colonization other than *Aspergillus*, 23 yeast colonization, 9 mixed fungal colonization, 5 BAL galactomannan positive without IPA and 81 with no fungal organisms in BAL.

• The BAL BDG distribution in the above categories is displayed in Table 2.

• The optimum cut-off of BDG for the diagnosis of IPA was 107 pg/ml with a sensitivity and specificity of 67% and 64% respectively (Figure 1).

Figure 1: Receiver operator characteristic (ROC) curve of (1, 3)-β-d-glucan in bronchoalveolar lavage for invasive aspergillosis in lung transplant recipients

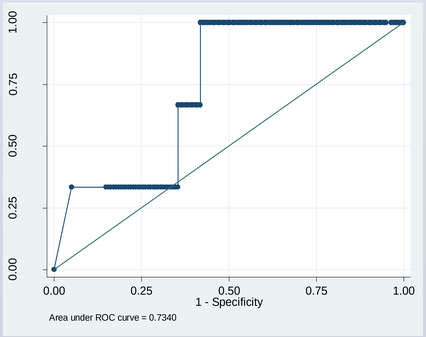

Table 1: Demographics of the 74 patients

Variables	Frequency N=74
Age (years)	
Median (IQR)	56 (33-63)
Male, n (%)	40 (54)
DLT, n (%)	63 (85)
Reason for transplant, n (%)	
ILD	29 (39)
COPD	18 (24)
Cystic fibrosis	18 (24)
Others	9 (13)
Event from day of transplant	
Median (days) (IQR)	189 (52-378)
CMV serostatus, n (%)	
D+/R-	19 (26)
R+	40 (54)
R-	11 (15)

IQR, Interquartile range; DLT, Double lung transplant; ILD, Interstitial lung disease; COPD, Chronic obstructive pulmonary disease; CMV, Cytomegalovirus; D, Donor; R, Recipient

Table 2: Distribution of BDG values in the BAL of lung transplant recipients in the various fungal categories

Categories	N	Median (pg/ml)	Interquartile range (pg/ml)
IPA	3	107.48	82.48 - 523,548
Respiratory colonization			
Aspergillus spp.	9	88.36	54.75 - 7812
Non *Aspergillus* mold	14	173.72	37.37 - 7812
Yeast	23	52.59	21.39 - 261.53
Mixed fungal	9	46.21	26.16 - 7812
None	81	41.6	24.91 - 108.47
BAL GM positive	5	120.25	36.2 - 221.79

IPA, Invasive pulmonary aspergillosis; BDG, (1, 3)-β-d-glucan; BAL, Bronchoalveolar lavage; GM, galactomannan

Conclusions

• To our knowledge this is the first study reporting the performance of BDG in BAL of lung transplant recipients.

• We had anticipated a higher number of invasive aspergillosis in our study. Due to the small number, we were unable to determine with certainty the sensitivity and specificity of the test.

• The median BDG values were not elevated in respiratory fungal colonization and therefore appear promising.

• Studies with higher numbers of invasive pulmonary aspergillosis are necessary.

References

1. Lamoth F et al. β-Glucan antigenemia assay for the diagnosis of invasive fungal infections in patients with hematological malignancies: a systematic review and meta-analysis of cohort studies from the Third European Conference on Infections in Leukemia(ECIL-3). Clin Infect Dis. 2012 Mar 1;54(5):633-43.

2. Alexander BD et al. The (1,3){beta}-D-glucan test as an aid to early diagnosis of invasive fungal infections following lung transplantation. J Clin Microbiol. 2010 Nov;48(11):4083-8.

3. Husain S et al. A 2010 working formulation for the standardization of definitions of infections in cardiothoracic transplant recipients. J Heart Lung Transplant. 2011 Apr;30(4):361-74.