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The effect of antifungal treatments on bronchoalveolar lavage galactomannan for the diagnosis of invasive fungal infections in patients with hematological malignancy: Single-center experience

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ABSTRACT

Background Invasive fungal infections (IFI) mainly caused by aspergillus species are one of the leading causes of death in patients undergoing immunosuppressive therapy for hematological malignancies. The presence of galactomannan in bronchoalveolar lavage fluid (BAL GM) is an important diagnostic marker. Some of the factors affecting the BAL GM are still unknown. Antifungal treatment administered before or after BAL also affect BAL GM results.

Methods To investigate the effect of BAL GM timing on the diagnosis of IFE, 100 patients receiving immunosuppressive therapy with hematological malignancy at the Uludağ University Faculty of Medicine, Hematology Department, and underwent BAL over a 3-year period with the suspicion of IFE as well as 127 BAL procedures of these patients were examined.

Results There were 70 patients who started antifungal therapy before BAL and 30 patients who did not. BAL GM was found positive in 33 (47.1%) of the 70 patients who received antifungal therapy compared to 22 (73.3%) of the 30 patients who did not receive antifungal therapy. There was a significant difference between the two groups in terms of BAL GM positivity ($p = 0.016$). Subsequently, 127 BAL procedures of these 100 patients were evaluated. When the second, third, and subsequent BAL procedures of the same patients were included in the study, BAL GM was positive in 41 (46.6%) of the 88 procedures in patients who received treatment before BAL and in 25 (64.1%) of the 39 procedures in patients who did not receive treatment before BAL. The rate of BAL GM positivity did not differ between groups ($p = 0.068$).

Conclusions The balance between reducing the risk by initiating early antifungal therapy and maximizing the diagnostic value of BAL GM should be evaluated individually for each patient.

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INTRODUCTION

Invasive fungal infections (IFIs), mainly caused by Aspergillus species, are one of the leading causes of death in high-risk patient groups, including patients with haematological malignancies receiving immunosuppressive therapy, and the diagnosis of IFI is fairly complex.[1,2] The galactomannan (GM) test in bronchoalveolar lavage (BAL) is an important diagnostic method for the diagnosis of invasive fungal aspergillosis in patients with haematological malignancies.[3] Guidelines generally advocate that aspergillosis be detected early and preferably before starting antifungal therapy. In clinical practice, Aspergillus treatment is usually initiated before bronchoscopy owing to delays caused by the patient, personnel, or equipment.[4] Extensive studies are needed to evaluate the use of GM screening after initiating antifungal therapy. Therefore, this study aimed to assess adult patients with haematological malignancies who underwent BAL for IFI and to conduct a retrospective analysis of the effect of BAL GM timing on IFI diagnosis.

MATERIAL AND METHODS

The study included 100 patients who received immunosuppressive therapy for haematological malignancy over three years in an university department of haematology, and their BAL results were evaluated. In all cases, IFI was confirmed by clinical, microbiological, and radiological findings according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC-MSGERC) diagnostic criteria.[3,5-6] The clinical and outpatient follow-ups of the patients were reviewed retrospectively. Patient files were retrieved from the medical archive.

Bronchoscopy and bronchoalveolar lavage

According to the clinical practice guidelines of the American Thoracic Society, BAL with fiberoptic bronchoscopy was performed in all patients with a pre-diagnosis of IFI. After completing all airway examinations, BAL was performed from the bronchus/segment identified by computerised tomography (CT). BAL was collected by administering 20 mL volumes of sterile saline (maximum 100–200 mL) to the selected bronchopulmonary segment, gently aspirating each portion with the bronchoscope placed in the wedge position, and immediately sending it to the laboratory for microbiological examination.[7]

GM antigen analysis

Optic density index (ODI) ≥1.0 was accepted as GM positivity in BAL results.[6]

Statistical analysis

The conformity of the data to a normal distribution was examined using the Shapiro-Wilk test. Continuous variables were presented as median (minimum–maximum) and mean±standard deviation. Comparisons between groups receiving antifungal therapy before and after BAL were made using the independent sample t-test. Categorical variables were expressed as n (%). Variables were compared between groups using the Chi-square, Fisher's exact chi-square, and Fisher-Freeman-Halton tests. Statistical analysis was conducted using the SPSS (IBM Corp. Release 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program, and $p<0.05$ was considered statistically significant in all analyses.

RESULTS

A total of 100 patients who were undergoing immunosuppressive therapy for haematological malignancy in our department over three years and 127 BAL procedures performed on these patients were evaluated. Initially, only the first BAL procedures were assessed (100 BAL procedures), and then all procedures (127 BAL procedures) performed on all patients were analysed. Of the 100 patients included, 31 were females, and 69 were males. The mean age of patients who received antifungal treatment before BAL was 52 years (21:75; 47.15±14.55), and the mean age of patients who did not receive treatment before BAL was 50 years (19:86; 45.88±18.57).

Of the 100 patients, 14 had a history of hematopoietic stem cell transplantation, three were evaluated for IFI at the time of hospitalisation for transplantation, and 83 patients had no history of transplantation. There was no significant difference between the two groups regarding age, gender, and hematopoietic stem cell transplantation ($p=0.916$, $p=0.647$, and $p=0.578$, respectively) (Table 1). The haematological malignancy diagnoses of the patients were summarised in Table 2.

Patients were evaluated based on HRCT findings

Table 1. Distribution of gender, age, and history of bone marrow transplant among those receiving antifungal treatment before and after BAL

	Treatment initiated before BAL (n: 70)	Treatment initiated after BAL (n: 30)	*P*-value
Gender			0.916[a]
Female	22 (31%)	9 (30%)	
Male	48 (69%)	22 (70%)	
Age	52 (21:75) (47.15±14.55)	50 (19:86) (45.88±18.57)	0.647[b]
Hematopoietic stem cell transplantation			0.578[c]
no history of transplantation	56 (80%)	27 (90%)	
hospitalization for transplantation	3 (4.3%)	0	
history of transplantation	11 (15.7%)	3 (10%)	

The data were expressed as n (%), median (minimum:maximum), and mean±standard deviation. BAL: bronchoalveolar lavage.
[a]: Pearson Chi-square Test, [b]: Mann-Whitney U Test, [c]: Fisher-Freeman-Halton Test.

for invasive pulmonary aspergillosis. While symptoms were observed in 96 patients, 4 patients had no symptoms. Suspicious high-resolution computed tomography (HRCT) findings were detected in the entire patient group that received treatment before BAL. Micronodule was detected in 17, macronodule was detected in 12, cavitation was detected in 5, and halo was detected in 5 patients. The most common HRCT findings were consolidation and ground-glass appearance, observed in 85 patients.

It was determined that all patients were under antibiotic therapy before BAL. Antifungal prophylaxis was given to 39 patients. At the time of prophylaxis, none of the patients received antibiotic therapy. The effects of antifungal prophylaxis on BAL GM were examined in these patients. BAL GM was positive in 17 (43.6%) of the 39 patients. In contrast, BAL GM was positive in 38 (62.30%) of the 61 patients who did not receive antifungal prophylaxis. There was no difference between the groups regarding BAL GM positivity (p=0.067). In 35 of the patients, posaconazole was used for prophylaxis. Four patients received prophylaxis with fluconazole. BAL GM was positive in 15 (42.90%) of the 35 patients who received posaconazole compared to 40 (61.5%) of the 65 patients who did not. There was no difference between the two groups regarding BAL GM positivity (p=0.073).

To understand the effect of starting antifungal treatment before BAL to reduce mortality on GM results, patients who received empiric preemptive treatment and those who did not were evaluated. In 70 patients, antifungal therapy was initiated before BAL. In contrast, 30 patients had not received antifungal therapy before BAL. Among 70 patients (some received two or more antifungal therapy regimens), 40 received classical amphotericin B, 34 received liposomal amphotericin B, eight received voriconazole, and 7 received caspofungin. BAL GM was positive in 33 (47.1%) of the 70 patients (GM median value: 2.05) who received antifungal therapy compared to 22 (73.3%) of the 30 patients (GM median value: 3.17) who did not receive antifungal therapy. There was a significant difference between the two groups regarding BAL GM positivity (p=0.016) (Table 3). BAL GM positivity was higher in patients who had not received antifungal treatment. Among the patients who received antifungal treatment before BAL, the

Table 2. Distribution of patients receiving antifungal treatment before and after BAL according to haematological malignancy diagnosis

Diagnosis	Treatment initiated before BAL (n: 70)	Treatment initiated after BAL (n: 30)
Acute myeloid leukemia	35 (50%)	14 (47%)
Acute lymphoid leukemia	22 (31%)	6 (20%)
Chronic lymphocytic leukemia	1 (1.5%)	1 (3%)
non-Hodgkin's lymphoma	6 (9%)	5 (17%)
Hodgkin's lymphoma	1 (1.5%)	1 (3%)
Multiple myeloma	3 (4%)	2 (7%)
Biphenotypic leukemia	1 (1.5) %	1 (3%)
Hairy cell leukemia	1 (1.5%)	0

BAL: bronchoalveolar lavage.

Table 3. Evaluation of GM positivity in patients after the first BAL procedure

BAL GM	Treatment initiated before BAL (n: 70)	Treatment initiated after BAL (n: 30)	*P*-value
Positive	33 (47.1%)	22 (73.3%)	0.016[a]

GM: galactomannan, BAL: bronchoalveolar lavage.
[a]: Pearson Chi-square test.

time to undergo BAL was 6 (4) (median [interquartile range]) days in BAL GM-negative patients and 5 (6) days in BAL GM-positive patients. No significant difference was found between the groups (p=0.899). In patients who received treatment before BAL (n: 67), no correlation was found between BAL GM level and the duration of treatment until BAL (r=0.030, p=0.829). Of the 100 patients, 36 were classified as possible, 53 as probable, and 11 as proven according to the EORTC/MSGERC diagnostic criteria.

The BAL GM results that were evaluated were from the patients' first BAL procedures. Subsequently, 127 BAL procedures on 100 patients were assessed. The following data were obtained when the second and third BAL procedures were included in the study. In the group that received treatment before BAL, BAL GM was positive in 41 (46.6%) and negative in 47 (53.4%) of the 88 procedures. In the group that did not receive treatment before BAL, BAL GM was positive in 25 (64.1%) of the 39 procedures and negative in 14 (35.9%). The rate of BAL GM positivity did not differ between patients who received antifungal therapy before BAL and those who received antifungal therapy after BAL (p=0.068) (Table 4).

Remission was observed in 38 of 100 patients, and eight were referred to the intensive care unit. The disease was stable in 17 patients, and 37 patients died. Among the 70 patients who started antifungal treatment before BAL, 28 had a fatal outcome, while among the 30 patients who began treatment after BAL, 9 had a fatal outcome.

DISCUSSION

Invasive aspergillosis is the most common IFI in immunosuppressed patients with haematological malignancies, particularly in patients with acute leukaemia and allogeneic hematopoietic stem cell transplantation, most commonly affecting the lungs.[8] Therefore, early and accurate diagnosis is critical for identifying patients requiring treatment and avoiding unnecessary toxicity and costs.[9,10] Early antifungal therapy can improve survival rates. BAL GM screening is recommended as a test that provides high-quality evidence in neutropenic patients. However, various aspects of this test need further investigation. These include the effect of antifungal therapy on this test.[11] Researchers emphasise the importance of conducting extensive studies to evaluate the diagnostic value of GM screening after starting antifungal therapy.[4] In different studies, the effects of antifungal treatment on BAL GM have been reported differently. While some studies have shown that antifungal therapy adversely affects BAL GM sensitivity, others have found no significant difference, and some have seen a trend toward increased sensitivity.[12]

In a previous study involving 20 patients and 31 BAL samples, GM was negative in patients who had received amphotericin-based therapy for more than two days.[13] In another study, BAL GM sensitivity was increased in patients receiving antifungal therapy for ≤2 days and decreased in patients receiving treatment for >2 days.[14] There have also been reports that active antifungal therapy reduces the sensitivity of BAL GM.[9] However, some studies report no difference in BAL GM sensitivity between patients receiving and not receiving antifungal therapy. The mean sensitivity

Table 4. Evaluation of 127 BAL procedures in 100 patients

BAL GM	Antifungal treatment		*P*-value
	Treatment initiated before BAL (n: 88)	Treatment initiated after BAL (n: 39)	
Negative	47 (53.4%)	14 (35.9%)	0.068[a]
Positive	41 (46.6%)	25 (64.1%)	

BAL: bronchoalveolar lavage, GM: galactomannan.
[a]: Pearson Chi-square test.

of BAL GM was not reduced by treatment.[10] Short-term antifungal agents did not affect BAL GM performance.[15] It was also reported that antifungal treatment negatively affected serum GM levels but had little effect on BAL GM.[16] According to one study, empiric antifungal therapy did not reduce BAL GM positivity, and patients who received antifungals for less than 48 hours had more widely positive BAL GM and higher median BAL GM levels.[17] Further studies are needed to understand the diagnostic value of BAL GM after initiating antifungal therapy.[2,4] The authors evaluated 48 patients with haematological malignancies and 62 BAL samples of these patients before and after BAL. It was reported that BAL GM results in lavages performed after the initiation of treatment were not adversely affected by the previous antifungal treatment. In contrast, a positive correlation was found associated with treatment-resistant fungal infection. Some GM results were positive even after 96 days of antifungal therapy. The authors concluded that previous antifungal treatment did not adversely affect BAL GM.[4]

The present study evaluated patients with IFI based on clinical, laboratory, and radiological findings. ODI ≥1 was accepted as GM positivity in BAL results. In the present study, there was no difference in BAL GM positivity between patients who did not receive antifungal prophylaxis and those who received antifungal prophylaxis before BAL. Regarding antifungal prophylaxis, there was no difference in BAL GM positivity between the two groups (p=0.067). In a previous study, patients who received antifungal prophylaxis and were thought to have IFI were evaluated. BAL GM was positive in 4/15 (27%) patients who did not receive prophylaxis with posaconazole and 6/11 patients (55%) who received prophylaxis with posaconazole. No significant difference was found between the groups (p=0.227). In contrast, the procedure was required in 15/34 patients (44%) not receiving posaconazole and 11/84 patients (13%) receiving posaconazole (p<0.001).[18]

It was determined that all patients had received antibiotherapy before BAL. In 70 patients, antifungal therapy was initiated before the first BAL procedure, whereas antifungal therapy was not initiated before the first BAL procedure in 30 patients. BAL GM positivity was higher in patients who had not received antifungal treatment. When the second and third BAL procedures of the same patients were also included in the evaluation, no significant difference was observed between the procedures in which antifungal treatment was initiated before BAL and the procedures in which antifungal treatment was initiated after BAL, which was consistent with the findings of other studies.[4]

Our study had limitations. All patients were under antibiotics at the initiation of antifungal therapy, and the impact of this treatment on the results has not been specifically investigated. Antifungal treatment should be initiated without delay in immunosuppressed patients. Delays in BAL procedures may occur due to technical issues, personnel issues, and other reasons. The impact of administering treatment before and after BAL on outcomes is controversial, and our research contributes to the literature in this regard.

CONCLUSIONS

In conclusion, conflicting literature reports on the effect of initiating antifungal therapy on BAL GM may be attributed to differences in study methods. According to the findings obtained in the present study, BAL procedures should be performed before starting antifungal treatment whenever possible to preserve the diagnostic value of BAL GM in the first febrile episode. When repeated BAL procedures are performed on the same patient, the effect of antifungal treatment on the diagnostic value of BAL GM disappears. BAL GM is an essential diagnostic tool in haematological malignancies with IFI. The balance between reducing the risk by initiating early antifungal therapy and maximising the diagnostic value of BAL GM should be evaluated individually for each patient.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Uludağ University, Bursa, Turkey. (Decision number: 2021-KAEK-26/173, date: 02.04.2019).

Authors' Contribution

Study Conception: MY, FÖ, BE, ED, MİK, VÖ; Study Design: MY, FÖ, BE, ED, MİK, VÖ; Literature Review: MY, FÖ, BE, ED, MİK, VÖ; Critical Review: FÖ, BE, VÖ; Data Collection and/or Processing: BE, MY; Analysis and/or Data Interpretation: MY, FÖ; Manuscript preparing: MY, FÖ.

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