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Evaluation of Empirical and Preemptive Therapy Approaches of Invasive Mold Infections in Patients with Hematologic Malignancy

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Abstract

Objective: We aimed to evaluate the diagnostic and therapeutic approaches of invasive mold infections in febrile neutropenic patients.

Methods: This retrospective and single-center study includes patients with hematologic malignancy and invasive mold infections. Predictors for 30-day and 1-year mortality were determined.

Results: A total of 87 patients were recorded. Of whom, 48 (55.2%) were male and the mean age was 44.56 ± 15.83. Twenty patients were in the empirical therapy group and 67 were in the preemptive group. Galactomannan positivity rate was found 24.1% (n = 21). The causative agents were detected in 16 patients. In the initial treatment, liposomal amphotericin B (n = 53), voriconazole (n = 27), caspofungin (n = 5), and posaconazole (n = 1) were used. The 30-day mortality rate was 26.4%, while the 1-year mortality rate was 44.8%. The 30-day (45.0% vs. 20.9%, $P = .03$) and 1-year (65% vs. 38.8%, $P = .04$) mortality rates were significantly higher in empirical treatment group than in preemptive treatment group. In multivariate analysis, presence of blasts in peripheral blood ($P = .04$, 95% CI = 1.01-9.38, odds ratio = 3.07) was determined as an independent risk factor for 30-day mortality. No independent risk factor was found for 1-year mortality.

Conclusion: As a result, despite the early initiation of empirical treatment, preemptive therapy approach was as effective as empirical approach in the management of invasive mold infections. Therefore, invasive and noninvasive diagnostic methods should be used more frequently to decrease overtreatment. In conclusion, current interdisciplinary approaches are crucial for evidence-based early diagnosis in immunocompromised patients with hematologic malignancies.

Keywords: Empirical therapy, hematologic malignancy, invasive mold infections, preemptive therapy

Introduction

Hematologic malignancies are neoplasms of myeloid and lymphoid cells, which comprise the most important components of the immune system. Febrile neutropenic infections are frequently observed during the course or treatment of hematologic malignancies. Infections due to *Aspergillus* spp. are the important causes of morbidity and mortality among immunocompromised patients, especially those receiving intensive chemotherapy and undergoing hematopoietic stem cell transplantation (HSCT) for hematologic malignancies.[1,2]

Invasive aspergillosis (IA) infection has been associated with mortality rates varying between 35.5% and 84.6%.[2-4] Delay in diagnosis based on standard culture-based and histopathological identification methods has been accused for these high mortality rates.[5,6] Empirical approach is recommended for patients with persistent fever under broad-spectrum antibiotics when they are at high risk for IA and have prolonged neutropenia. Preemptive treatment is an alternative approach to empirical treatment in order to reduce unnecessary antifungal therapy.[7] There is a limited number of studies on antifungal treatment approaches of invasive fungal infections in patients with hematologic malignancy. Most studies have evaluated invasive yeast infections and invasive mold infections (IMIs) together, although this fungal infections have different clinical features. In this study, we aimed to evaluate the short-term and long-term clinical outcomes of IMIs, and to compare the diagnostic and therapeutic approaches of IMIs in hematologic malignancies.

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Methods

In this single-center study, inpatients followed up at the Adult Hematology Department and consulted by the Infectious Diseases and Clinical Microbiology Department between January 2015 and January 2019 were retrospectively screened. Information on the type of malignancy, depth, and duration of neutropenia before the

antifungal treatment, duration of fever, biochemical, microbiological and radiological results, the use of antifungal prophylaxis and treatments, and clinical outcomes was recorded via a follow-up data sheet.

A total of 87 patients with active hematologic malignancies treated with antifungal agents against IMIs during a febrile neutropenic episode were included. Febrile neutropenia was defined as a single oral temperature of ≥38.3°C or 2 consecutive measures of ≥38.0°C for 1 hour and an absolute neutrophil count of less than 1.0×10^9/L. or expected to fall below 0.5×10^9/L. Severe neutropenia was defined as absolute neutrophil count of less than 0.5×10^9/L, and profound neutropenia was defined as absolute neutrophil count of less than 0.1×10^9/L.[8]

Therapeutic approaches were evaluated according to the clinical, laboratory, and radiological results. Empirical approach was defined as administration of an antifungal treatment to a neutropenic patient with persistent or recurrent fever (≥96 hours) despite adequate antibacterial therapy without a known source of infection. Preemptive treatment was defined as administration of an antifungal agent to patients with clinical, laboratory, radiological findings, or galactomannan (GM)-antigen-assay evidence suggesting IMIs.

Fungal samples were evaluated by microscopic/macroscopic examinations and analyses by API 20C AUX (bio-Mérieux, France) and "matrix-assisted laser desorption ionization time of flight mass spectrometry" methods. Antifungal susceptibility patterns were determined using minimum inhibitory concentration (MIC) results in Roswell Park Memorial Institute 1640 medium and results were interpreted according to European Committee on Antimicrobial Susceptibility Testing standards. Serum and bronchoalveolar lavage (BAL) GM cut-off values were determined according to the European Organization for Research and Treatment of Cancer and Mycoses Study Group 2019 criteria.[9]

Statistical Analysis

The analyses were performed using Statistical Package for Social Sciences version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). The Mann–Whitney *U*-test and independent-sample *t* test were used to compare the 2 groups in terms of the continuous variables. Categorical data were compared with chi-square test or Fischer's exact test. A *P*-value <.05 was considered as statistically significant. To evaluate the factors in the 30-day and 1-year mortality, univariate and multivariate logistic regression analysis was performed.

Results

A total of 87 patients were enrolled. Of whom, 48 (55.2%) were male and the mean age was 44.56 ± 15.83 years. Twenty patients were in the empirical therapy group and 67 were in the preemptive group. Among the 87 patients, 44 (50.6%) had acute

Table 1. Demographic Characteristics in Patients with IMI

	Total (n = 87)		Empirical Treatment (n = 20)		Preemptive Treatment (n = 67)		
	n	%	n	%	n	%	*P*
Age							
Mean ± SD	44.56 ± 15.83		47.95 ± 15.48		43.55 ± 15.91		.343
Median	45		52		44		
Gender							
Male	48	55.2	9	45.0	39	58.2	.297
Female	39	44.8	11	55.0	28	41.8	
Neutrophil count (at the initiation of treatment)							
<100 mm³	51	58.6	7	35.0	44	65.6	**.015**
<500 mm³	60	69.0	10	50.0	50	74.6	**.037**
500-1000 mm³	27	31.0	10	50.0	17	25.3	**.041**
Duration of neutropenia							
<100 mm³ (>10 days)	36	41.4	5	25.0	31	46.2	.090
<500 mm³ (>10 days)	42	48.3	7	35.0	35	52.2	.176
Blasts in peripheral blood							
Yes	21	24.1	8	40.0	13	19.4	.064
No	66	75.9	12	60.0	54	80.6	
Underlying malignancy							
AML	44	50.6	3	15.0	12	17.9	.762
ALL	15	17.2	10	50.0	34	50.7	.953
HSCR	11	12.6	3	15.0	8	11.9	.718
Aplastic anemia	4	4.6	2	10.0	2	2.9	.189
KLL	4	4.6	0	0	4	5.9	.263
NHL	4	4.6	0	0	4	5.9	.263
Others	5	5.7	2	10.0	3	4.4	.352

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; HSCR, hematopoietic stem cell recipient; IMI, invasive mold infection; KLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma.

Table 2. Antifungal Susceptibility Data of Pathogens Isolated in Culture

	A. fumigatus	*A. flavus*	*A. fumigatus*	*Aspergillus* spp.	*A. fumigatus*	*A. fumigatus*	*Aspergillus* spp.	*A. fumigatus*	*A. flavus*	*A. flavus*
Patient number	6	13	21	33	41	47	55	62	68	77
Type of specimens	BAL	Sinus biopsy	Sputum	BAL	BAL	Nasal biopsy	Nasal biopsy	BAL	Sinus biopsy	Sinus biopsy
Posaconazole	0.25	0.064	0.064	0.047	0.125	0.19	0.064	0.125	0.094	0.064
Voriconazole	0.25	0.094	–	0.19	0.38	0.50	0.19	0.75	0.19	0.125
Amphotericin B	1	6	0.50	4	0.50	0.50	2	1	2	4
Caspofungin	0.032	0.38	0.38	–	–	0.25	0.75	–	0.125	0.50
Micafungin	0.016	-	0.003	0.012	0.003	–	0.016	–	0.064	–
Anidulofungin	–	0.094	–	0.016	0.003	–	0.047	0.125	–	0.008

BAL, bronchoalveolar lavage.

myeloid leukemia (AML), 15 (17.2%) had acute lymphocytic leukemia (ALL), 4 (4.6%) had chronic lymphocytic leukemia, 1 had chronic myelomonocytic leukemia, 4 had non-Hodgkin's lymphoma, 1 had Hodgkin's lymphoma, 4 had aplastic anemia, 1 had plasma cell leukemia, and 2 had acute leukemia (not specified). Eleven (12.6%) patients underwent HSCT. The neutrophil count at the time of antifungal treatment was ≤500 cells/mm^3 in 60 patients (69.0%) and ≤100 cells/mm^3 in 51 patients (58.6%). The neutropenia over 10 days before antifungal treatment was detected in 42 patients (48.3%). Blasts in peripheral blood were detected in 21 patients (24%). At the initiation of treatment, severe (50.0% vs. 74.6%, *P* = .037) and profound (35.0% vs. 65.6%, *P* = .015) neutropenia were less frequent in the empirical treatment group than in the preemptive treatment group. Blasts in peripheral blood were more frequent in the empirical treatment group than in the preemptive treatment group, but no significant difference was observed (40.0% vs. 19.4%, *P* = .064) (Table 1).

Causative agents were detected in 16 patients (*Aspergillus fumigatus* in 8, *A. flavus* in 4, *Aspergillus* spp. in 3, and *Fusarium* spp. in 1). The fungal pathogens in BAL of 6 patients, sputum specimens of 3 patients (3 consequent in 1 patient, 2 consequent in 2 patients), nasal biopsy samples of 3 patients, and mucosal sinus biopsy/aspirate of 3 patients were obtained. Additionally, 1 fungal pathogen was detected after pathological examinations in a patient. When the respiratory tract samples were examined, *A. fumigatus* was isolated in 8 cultures, and *A. flavus* was isolated only in 1 culture. In 7 cultures obtained from mucosal sinus aspirates and nasal biopsy specimens, *A. flavus* in 3 cultures, *Aspergillus* spp. in 3 cultures, and *Fusarium* spp. in 1 culture were isolated. While *A. fumigatus* was frequently isolated in patients with pulmonary aspergillosis, *A. flavus* species were isolated in patients with fungal sinusitis. Antifungal susceptibility data in 10 of the 16 fungal pathogens isolated in culture are shown in Table 2.

Galactomannan positivity rate was found 24.1% (n = 21). Serum and BAL GM were positive in 13 and 6 patients, respectively. In 2 patients both serum and BAL GM were positive. Repeated serum GM negativity was detected in 6 patients with positive BAL results (Table 3). Serum GM levels were detected negative in 14 (93.3%) of the patients after the initiation of antifungal therapy.

Fifty-five patients received fluconazole prophylaxis, 6 patients received voriconazole prophylaxis and 3 patients received posaconazole prophylaxis. The use of antifungal prophylaxis was not detected in 23 patients diagnosed with hematologic malignancy at the time of antifungal therapy was initiated. In the initial treatment, liposomal amphotericin B in 53 patients, voriconazole in 27 patients, caspofungin in 5 patients, and posaconazole in 1 patient were used. There was only 1 patient that received liposomal amphotericin B + voriconazole combination. An antifungal switch was detected in 31 (36%) patients. Voriconazole was switched to liposomal amphotericin B in 2 of these patients due to acute renal failure, in another 2 of these patients due to hepatotoxicity, and in 1 patient due to drug interaction with a chemotherapeutic agent. Liposomal amphotericin B treatment was switched to voriconazole + caspofungin in 1 patient due to allergic reaction, switched to voriconazole in 1 patient due to tubulopathy, and switched to voriconazole in 3 patients due to antifungal resistance during the follow-up. Caspofungin was added to liposomal amphotericin B treatment in 1 patient. In the remaining 20 patients, antifungal therapy was switched due to no clinical or radiological response.

The 30-day mortality rate was 26.4%, while the 1-year mortality rate was 44.8%. Age was associated with 30-day (*P* = .03) and 1-year (*P* = .04) mortality. The 30-day (*P* = .03) and 1-year (*P* =

Table 3. Bronchoalveolar Lavage Fluid and Serum Galactomannan Antigen Levels

Patients	BAL GM	Serum GM	Culture
9	Positive (9.9)	Negative	Negative
24	Positive (7.7)	Negative	Negative
41	Positive (6.6)	Positive (2.3)	*A. fumigatus*
49	Positive (4.2)	Negative	*A. fumigatus*
57	Positive (6.2)	Positive (3.1)	Negative
68	Positive (10)	Negative	*A. flavus*
74	Positive (2.7)	Negative	Negative
81	Positive (1)	Negative	Negative

BAL, bronchoalveolar lavage; GM, galactomannan.

Table 4. Predictors for the 30-Day and 1-Year Mortality in Patients with Invasive Mold Infections

	30-Day Mortality					1-Year Mortality				
	Presence		Absence			Presence		Absence		
	n	(%)	n	(%)	*P*	n	(%)	n	(%)	*P*
Age										
Mean	50.9 ± 15.1		42.3 ± 15.6		**.03**	48.1 ± 16.2		41.7 ± 15.1		**.04**
Median	55		41.5			51		39.5		
Gender										
Male	16	33.3	32	66.7	.10	23	47.9	25	52.1	.52
Female	7	17.9	32	82.1		16	41.0	23	59.0	
Neutrophil count (at the initiation of treatment)										
<100	9	17.6	42	82.4	**.03**	18	35.3	33	64.7	**.03**
<500	11	18.3	49	81.7	**.01**	21	35.0	39	65.0	**.01**
Blast	10	47.6	11	52.4	**.01**	14	66.7	7	33.3	**.02**
Neutrophil count (>10 days before the antifungal treatment)										
<100	5	13.9	31	86.1	.19	11	30.6	25	69.4	.18
<500	7	16.7	35	83.3	.41	14	33.3	28	66.7	.31
Mold-active antifungal prophylaxis										
Presence	3	33.3	6	66.7	.62	6	66.7	3	33.3	.07
Absence	20	25.6	58	74.4		33	42.1	45	57.9	
Identified mold isolates										
Positive	3	24.1	14	75.7	.36	6	35.3	11	64.7	.38
Negative	20	28.6	50	71.4		33	47.1	37	52.9	
Galactomannan levels										
Positive	7	33.3	14	66.7	.41	12	57.1	9	42.9	.19
Negative	16	24.2	50	75.8		27	40.9	39	59.1	
Antifungal therapy										
Empirical	9	45.0	11	55.0	**.03**	13	65.0	7	35.0	**.04**
Preemptive	14	20.9	53	79.1		26	38.8	41	61.2	
Underlying malignancy										
HSCR	2	18.2	9	81.8	.51	6	54.5	5	45.5	.49
AML/ALL	16	27.1	43	72.9	.83	25	42.4	34	57.6	.50
AML	10	22.7	34	77.3	.42	18	40.9	26	59.1	.46

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; HSCR, hematopoietic stem cell recipient.

.04) mortality rates were significantly higher in patients receiving empirical treatment. The 30-day mortality (*P* = .01) and 1-year mortality (*P* = .02) were higher in patients with presence of blasts in peripheral blood. Mortality was higher in patients with positive GM and among male gender, but no statistically significant difference was found. Underlying malignancy, neutropenia (>10 days), and identified isolates were not associated with mortality (Table 4).

In multivariate regression analysis, presence of blasts in peripheral blood (*P* = .04, 95% CI = 1.01-9.38, odds ratio = 3.07) was determined as an independent risk factor for 30-day mortality (Table 5). No independent risk factor was found for 1-year mortality (Table 6).

Discussion

Invasive fungal infections are important causes of mortality and morbidity in febrile neutropenic patients. While the incidence of invasive candidiasis have decreased in recent years, IA has gradually become a major problem.[10] Despite appropriate and effective antifungal treatment in *Aspergillus* infections, mortality rates are still high.[11] Early diagnosis of IMIs is very important in order to increase treatment success rates.[12] On the other hand, an empirical

Table 5. Univariate and Multivariate Regression Analyses for 30-Day Mortality in Patients with Invasive Mold Infections

	Univariate Regression			Multivariate Regression		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age	0.96	0.93-0.99	**.03**	0.97	0.94-1.00	.06
Presence of blast	3.71	1.30-10.58	**.01**	**3.07**	1.01-9.38	**.04**
Empirical treatment	3.09	1.07-8.94	**.04**	2.37	0.76-7.37	.14

OR, odds ratio.

Table 6. Univariate and Multivariate Regression Analyses for 1-Year Mortality in Patients with Invasive Mold Infections

	Univariate Regression			Multivariate Regression		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age	0.97	0.94-1.00	.07	0.97	0.95-1.00	.12
Presence of blast	3.71	1.29-10.58	**.02**	2.81	0.95-8.30	.06
Empirical treatment	2.93	1.03-8.30	**.04**	2.32	0.78-6.94	.13

OR, odds ratio.

treatment approach is often recommended to ensure an early treatment in high-risk patients.[13] There are some studies comparing empirical and preemptive therapy approaches on mortality.[13-16] In the randomized clinical study of Satolaya et al,[13] while mortality was 8% in the empirical treatment group, it was 5% in the preemptive group. They found that mortality was not significantly different between 2 treatment approaches (P = .97). In another randomized controlled study,[14] mortality was found to be 3% in the empirical treatment group, and 5% in the preemptive group, but no statistically significant difference was found. Pagano et al[15] showed that mortality rates were significantly lower in the empirical treatment group than in the preemptive group (7% vs. 21%, P = .002). In the meta-analysis of Fung et al,[16] they demonstrated that pre-emptive treatment approach reduced the use of antifungal agents without increasing mortality. Additionally, there are some studies showing that the presence of blasts in peripheral blood and bone marrow blasts are associated with poor prognosis and mortality.[17,18]

Our study showed that despite the early initiation of empirical treatment, treatment failure and mortality rates remained higher in the empirical treatment group. The rates of 30-day and 1-year mortality in our study group justified life-threatening impact of IMIs in patients with hematologic malignancies. In the empirical treatment group, it was seen that half of patients died within 30 days and 2 out of 3 patients died within 1 year. However, empirical or preemptive therapy approaches were not independent predictors for mortality. In the present study, multivariate regression analysis revealed that the presence of blasts in peripheral blood were determined as an independent risk factor for 30-day mortality.

Despite the early initiation of empirical treatment without ruling out IMIs possibility, treatment failure and high mortality rates may be thought to result from underlying hematologic disease severity, shock of unknown origin, and severe respiratory distress.[19] Additionally, the higher frequency of blasts in peripheral blood (n = 8, 40%), which was an independent risk factor for mortality in our study, in the empirical treatment group may cause the higher mortality rates.

Serum GM antigen monitoring may be a useful method for the diagnostic evaluation.[20] In our study, GM levels in 21 patients contributed directly to the diagnosis of the IMIs. Positive culture results were obtained in only 6 of 21 patients with positive GM results. Also, serum GM levels may be used as a marker for the treatment follow-up.[21] In our study, it was observed that after appropriate antifungal therapy, consecutive GM levels were negative in all patients except 1 patient.

Bronchoalveolar lavage GM positivity was found in 8 of the patients. Fungal agents in the culture were also found in 3 of these patients. In 6 out of 8 patients with positive BAL GM testing results, serum GM levels were found negative in the repeated testing. In the study of Zhou et al,[22] when the GM optical limit value was considered ≥0.5, BAL GM sensitivity was approximately 76% and serum GM sensitivity was 38% (P = .001). Similar results have been obtained in other studies.[20,23] Moreover, in the meta-analysis of Zou et al,[24] BAL GM sensitivity was lower than serum GM sensitivity. When the current results are taken into consideration, it is understood that in fungal infections which are difficult to make diagnosis, invasive procedures such as BAL, sinus biopsy are needed for accrued diagnosis during the early stages of IMIs.

In the present study, MIC levels of amphotericin B in 3 *A. flavus* strains were detected as 2, 4, and 6 µg/mL. Higher MIC levels of amphotericin B in *A. flavus* strains observed in other studies were also found to be similar with our study.[25,26] These reports support that *A. flavus* may be intrinsically resistant to amphotericin B. However, the mechanisms of amphotericin B resistance in *A. flavus* are unknown. It is thought that this is probably due to increased levels of ergosterol and enzymatic activity of superoxide dismutase and peroxidase.[25] Minimum inhibitory concentration levels of voriconazole against these strains were found to be very low as 0.094, 0.19, 0.125 µg/mL. In a study investigated antifungal susceptibility, 5 *A. fumigatus* strains were found susceptible against amphotericin B with the MIC values of 0.5, 0.5, 0.5, 1, and 1 µg/mL. In our study, amphotericin B MIC levels were found to be high (2 and 4 µg/mL) in *Aspergillus* spp., consistent with the findings of Reichert-Lima et al[27] amphotericin B has been primarily preferred for suspected fungal sinusitis as Mucorales is the primary causative pathogen. However, in our study, as the fungi in the Mucorales family were relatively less prevalent in our unit and the predominant species was *A. flavus* such factors should be taken into consideration in managing empirical treatment.

This study has some limitations. First, it was conducted retrospectively in a single center. The results are not broadly applicable to many different types of people and situations, because differences in applications of the treatment, prophylaxis, and infection control policies between centers may affect the results. Second, we did not consider underlying comorbid diseases other than hematological malignancies as risk factors. However, we included underlying hematologic malignancies to a multivariate regression analysis. Therefore, we need new large-scale studies that address diagnostic and therapeutic problems in this area.

Conclusion

As a result, preemptive antifungal therapy was as effective as the empirical antifungal therapy for IMIs in patients with hematologic malignancy. Clinicians should mitigate unnecessary use of antifungals which may cause side effects, drug–drug interactions, and health expenditures. Therefore, invasive and non-invasive

diagnostic methods should be used more frequently to decrease overtreatment. In conclusion, current interdisciplinary approaches are crucial for evidence-based early diagnosis in immunocompromised patients with hematologic malignancies.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Clinical Research (Approval no: 151641, Date: 17/11/2020).

Informed Consent: Written informed consent was waived, given the retrospective nature of this study.

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References

1. Subirà M, Martino R, Franquet T, et al. Invasive pulmonary aspergillosis in patients with hematologic malignancies: survival and prognostic factors. *Haematologica*. 2002;87(5):528-534.
2. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica*. 2006;91(8):1068-1075.
3. Upton A, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. *Clin Infect Dis*. 2007;44(4):531-540. [CrossRef]
4. Neofytos D, Horn D, Anaissie E, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of multicenter Prospective Antifungal Therapy (PATH) alliance registry. *Clin Infect Dis*. 2009;48(3):265-273. [CrossRef]
5. Reichenberger F, Habicht J, Matt P, et al. Diagnostic yield of bronchoscopy in histologically proven invasive pulmonary aspergillosis. *Bone Marrow Transplant*. 1999;24(11):1195-1199. [CrossRef]
6. Jantunen E, Piilonen A, Volin L, et al. Diagnostic aspects of invasive Aspergillus infections in allogeneic BMT recipients. *Bone Marrow Transplant*. 2000;25(8):867-871. [CrossRef]
7. Patterson TF, Thompson GR, Denning DW, et al. Executive summary: practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. *Clin Infect Dis*. 2016;63(4):433-442. [CrossRef]
8. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol*. 2018;36(14):1443-1453. [CrossRef]
9. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the mycoses study group education and research consortium. *Clin Infect Dis*. 2020;71(6):1367-1376. [CrossRef]
10. Chamilos G, Luna M, Lewis RE, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989-2003). *Haematologica*. 2006;91(7):986-989.
11. Gallien S, Fournier S, Porcher R, et al. Therapeutic outcome and prognostic factors of invasive aspergillosis in an infectious disease department: a review of 34 cases. *Infection*. 2008;36(6):533-538. [CrossRef]
12. Dib RW, Hachem RY, Chaftari AM, Ghaly F, Jiang Y, Raad I. Treating invasive aspergillosis in patients with hematologic malignancy: diagnostic-driven approach versus empiric therapies. *BMC Infect Dis*. 2018;18(1):656. [CrossRef]
13. Santolaya ME, Alvarez AM, Acuña M, et al. Efficacy of pre-emptive versus empirical antifungal therapy in children with cancer and high-risk febrile neutropenia: a randomized clinical trial. *J Antimicrob Chemother*. 2018;73(10):2860-2866. [CrossRef]
14. Cordonnier C, Pautas C, Maury S, et al. Empirical versus preemptive antifungal therapy for high-tisk, febrile, neutropenic patients: a randomized, controlled trial. *Clin Infect Dis*. 2009;48(8):1042-1051. [CrossRef]
15. Pagano L, Caira M, Nosari A, et al. The use and efficacy of empirical versus pre-emptive therapy in the management of fungal infections: the HEMA e-Chart Project. *Haematologica*. 2011;96(9):1366-1370. [CrossRef]
16. Fung M, Kim J, Marty FM, Schwarzinger M, Koo S. Meta-analysis and cost comparison of empirical versus pre-emptive antifungal strategies in hematologic malignancy patients with high-risk febrile neutropenia. *PLoS One*. 2015;10(11):e0140930. [CrossRef]
17. Short NJ, Benton CB, Chen HC, et al. Peripheral blood blast clearance is an independent prognostic factor for survival and response to acute myeloid leukemia induction chemotherapy. *Am J Hematol*. 2016;91(12):1221-1226. [CrossRef]
18. Liu CJ, Hong YC, Kuan AS, et al. The risk of early mortality in elderly patients with newly diagnosed acute myeloid leukemia. *Cancer Med*. 2020;9(4):1572-1580. [CrossRef]
19. Rüping MJGT, Vehreschild JJ, Cornely OA. Patients at high risk of invasive fungal infections: When and how to treat. *Drugs*. 2008;68(14):1941-1962. [CrossRef]
20. Gupta A, Capoor MR, Shende T, et al. Comparative evaluation of galactomannan test with bronchoalveolar lavage and serum for the diagnosis of invasive aspergillosis in patients with hematological malignancies. *J Lab Physicians*. 2017;9(4):234-238. [CrossRef]
21. Mercier T, Guldentops E, Lagrou K, Maertens J. Galactomannan, a surrogate marker for outcome in invasive aspergillosis: finally coming of age. *Front Microbiol*. 2018;9:661. [CrossRef]
22. Zhou W, Li H, Zhang Y, et al. Diagnostic value of galactomannan antigen test in serum and bronchoalveolar lavage fluid samples from patients with nonneutropenic invasive pulmonary aspergillosis. *J Clin Microbiol*. 2017;55(7):2153-2161. [CrossRef]
23. Wu Z, Wang L, Tan L, Wu J, Chen Z, Hu M. Diagnostic value of galactomannan in serum and bronchoalveolar lavage fluid for invasive pulmonary aspergillosis in non-neutropenic patients. *Diagn Microbiol Infect Dis*. 2021;99(4):115274. [CrossRef]
24. Zou M, Tang L, Zhao S, et al. Systematic review and meta-analysis of detecting galactomannan in bronchoalveolar lavage fluid for diagnosing invasive aspergillosis. *PLoS One*. 2012;7(8):e43347. [CrossRef]
25. Taylor E, Ferreira G, Freitas G, Ferreira R, de Assis Santos D, de Resende-Stoianoff M. Screening of antifungal susceptibility in cave-dwelling aspergilli and report of an amphotericin B-resistant Aspergillus flavus. *Int J Speleol*. 2017;46(3):369-378. [CrossRef]
26. Rudramurthy SM, Paul RA, Chakrabarti A, Mouton JW, Meis JF. Invasive Aspergillosis by Aspergillus flavus: epidemiology, Diagnosis, antifungal Resistance, and Management. *J Fungi (Basel)*. 2019;5(3):55. [CrossRef]
27. Reichert-Lima F, Lyra L, Pontes L, et al. Surveillance for azoles resistance in Aspergillus spp. highlights a high number of amphotericin B-resistant isolates. *Mycoses*. 2018;61(6):360-365. [CrossRef]