Invasive Fungal Infections in Children With Acute Myeloid Leukemia: A Single-center Experience Over 19 Years

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Objective: Invasive fungal infections (IFIs) remain a significant cause of morbidity and mortality in children with acute myeloid leukemia (AML). This study aimed to evaluate the incidence, risk factors, etiology, and outcome of IFIs in children with AML and the effect of mold-active antifungal prophylaxis.

Materials and Methods: We retrospectively reviewed pediatric patients treated for AML between January 2004 and December 2022. Proven, probable, or possible IFIs were defined using standardized definitions of the European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) classification published at 2008.

Results: A total of 298 febrile neutropenia episodes from 78 patients were evaluated. Proven, probable, and possible IFI rates were 3%, 2.6%, and 9.4%, respectively. Profound neutropenia was detected in 18 (58%) and prolonged neutropenia in 20 (64.5%) of the IFI episodes.. Invasive aspergillosis accounted for the majority of IFI episodes; however, non-albicans *Candida* spp. were the most isolated pathogens in the proven group. Patients with relapsed AML were particularly at risk for the development of IFI ($P=0.02$). A significant decrease in IFI episodes was achieved with mold-active antifungal prophylaxis with voriconazole ($P=0.01$, odds ratio: 0.288, %95 CI:0.104-0.797). The overall mortality was 35.8%, and the IFI-attributable mortality rate was 25%. In the multivariate analysis, relapsed disease was the most significant risk factor associated with mortality ($P=0.006$, odds ratio:4.745; 95% CI: 1.573-14.316).

Conclusion: Mold-active prophylaxis reduced the rate of IFIs in this cohort however IFI-related mortality was still high as 25% in pediatric AML patients. Relapsed AML was the most significant risk factor associated with mortality.

Key Words: invasive fungal infection, acute myeloid leukemia, febrile neutropenia, child

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Invasive fungal infections (IFIs) are one of the leading causes of morbidity and mortality in children with acute myeloid leukemia (AML).[1] The incidence of IFIs has increased due to intensive chemotherapy regimens resulting in prolonged and profound neutropenia.[2] Previous data on IFIs in immunocompromised hosts are mostly from adult series. Varying IFI rates have been reported in childhood according to the prophylactic antifungal regimens and the type of leukemia. The incidence of IFIs in children with hematologic malignancies ranged between 1.7% and 35.4% in previous studies.[3–6] The cumulative incidence of IFIs in pediatric AML patients has been demonstrated as 5% to 13%, and IFIs were found to be an attributable cause of death in 5% to 18% of the patients.[7–9]

Despite developing new antifungal agents and prophylactic antifungal strategies, diagnostic technological advances [b-glucan, galactomannan assays, lateral-flow device, and fungus polymerase chain reaction]; early diagnosis and treatment of IFIs are still challenging for clinicians. IFIs are associated with poor outcomes; in recent studies, the rate of IFIs-related mortality ranged between 20% and 70%.[3,10,11] In a study evaluating pediatric AML, the overall mortality of IFIs was reported as high as 53% over 10 years, and patients with pulmonary Aspergillosis lead to the highest mortality (80%).[12]

Patients with AML, relapsed leukemia, allogeneic hematopoietic stem cell recipients with persistent fever (>96 h), prolonged neutropenia (>10 d), those receiving a high dose of glucocorticoids, patients undergoing highly immunosuppressive regimens for other malignancies, transplantations or autoimmune diseases are at high risk for developing IFIs.[4]

This study aimed to retrospectively evaluate the clinical characteristics, risk factors, incidence and outcome of IFIs and to present the effect of mold-active antifungal prophylaxis.

MATERIALS AND METHODS

Pediatric patients (younger than or equal to 18 years old) diagnosed with AML and treated at the Pediatric Hematology Department of Medical School of Ege University between January 2004 and December 2022 were included in this study. We retrospectively evaluated the medical records of 78 pediatric AML patients. Patients were treated according to AML BFM 98, 2004 or 2013 protocols. Patients' demographics (sex, age, the French-American-British (FAB) morphological classification and risk classification of the disease, history of relapse, hematopoietic stem cell transplantation [HSCT]) and clinical characteristics, laboratory findings including radiological, histological, and microbiological findings, antifungal prophylaxis, medications, and outcome were obtained from medical records.

In addition to acute leukemia, patients had to have a fungal infection defined according to the 2008 version of the European Organization for Research and Treatment of

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Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG).[4] Proven IFI was defined by one of the following: (i) mold or 'black yeast' organism obtained directly from a blood or sterile site culture, excluding bronchoalveolar lavage (BAL) fluid, a specimen from a cranial sinus cavity or urine or (ii) demonstration of hyphae or melanized yeast-like forms by histopathology, cytopathology or direct microscopy. Probable IFI was defined as the presence of combined host factors, clinical features and mycological evidence. All patients met the host factor criteria. Host factors included;

- Recent history of neutropenia ($<0.5\times109$ neutrophils/L [<500 neutrophils/mm^3] for >10 d) temporally related to the onset of fungal disease.
- Receipt of an allogeneic stem cell transplant.
- Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/ day of prednisone equivalent for >3 weeks.
- Treatment with other recognized T-cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogs during the past 90 days.
- Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency).

Possible IFI was defined in cases that meet the criteria for a host factor and the clinical criterion without a mycological criterion.

Febrile neutropenia was empirically treated with piperacillin-tazobactam or meropenem with amikacin. If the patient was hemodynamically unstable, a glycopeptide was empirically added. Thorax computed tomography (CT) was performed in addition to sinus CT if there was a clinical suspicion of fungal sinusitis. Abdominal ultrasound and CT scans were performed if there was a clinical suspicion of IFI. For deaths occurring within 12 weeks after a diagnosis of IFI, information was collected regarding the cause of death and its relationship with the active fungal disease. All deaths occurring within 3 months of IFI diagnosis were defined as crude mortality, and deaths occurring within 15 days of IFI and fungemia were considered as attributable mortality.

Neutropenia was defined as an absolute neutrophil count <500/mm^3, profound neutropenia was defined as absolute neutrophil count <100/mm^3, and prolonged neutropenia was defined as the neutropenia period lasting longer than 14 days. Serum galactomannan (GM) levels were measured twice weekly during febrile neutropenia episodes before the initiation of empirical antifungal treatment in case of possible, probable, or proven invasive aspergillosis (IA) by using enzyme immunoassay method. Serum GM test results with an optical density index ≥ 0.5 was considered positive. Antifungal prophylaxis, empirical antifungal therapy, and changes in antifungal agents were recorded.

The patients received mold-active antifungal prophylaxis from the first day of their neutropenia period. In our center, mold-active antifungal prophylaxis with voriconazole was started in 2013. Liposomal Amphotericin B (L-AMB) was given intermittently during chemotherapy, but intravenous voriconazole was the first choice if fever occurred. Treatment revision was made according to the antifungal susceptibility results.

Ethical Approval

This study was done with the approval decision of the Ege University Clinical Research Ethics Committee dated 02.01.2023 and numbered 22-12.2T/9.

Statistical Analysis

Descriptive statistics were used to describe the data, and analysis of the results was performed using the statistical program SPSS (version 24.0). Data were expressed as means ± SD or medians for continuous variables or percentages for categorical variables. The categorical variables are expressed as numbers (n) and percentages (%).The univariate analyses to identify risk factors for IFIs was investigated using χ^2 Fisher exact, Student's t and Mann-Whitney U tests, where appropriate. A p value of 0.05 was used to determine the statistical significance of differences and correlations. For the multivariate analysis, the possible factors identified with univariate analysis were further entered into logistic regression analysis to determine independent risk factors of mortality.

RESULTS

Patient Characteristics

During 19 years, 78 children diagnosed with AML were treated at the Pediatric Hematology Department of Ege University, Turkey. Forty patients were male (51.3%), and 38 (48.7%) were female. The median age was 123 months (range 1 to 219 mo). According to the AML Berlin-Frankfurt-Munster (BFM) study group classifications, 33 (42.3%) of the patients were classified as standard risk, 7 (9.85%) as medium risk, and 38 (48.7%) as high risk. Relapse occurred in 25 (32%) patients who underwent HSCT. IFI developed in 28 children (35.8%). The median age of patients in the IFI group was older (165.5 [interquartile range:135] mo) ($P<0.05$). No significant difference was determined in terms of sex ($P>0.05$). The characteristics of the patients with IFI and non-IFI are summarized in Table 1.

Classification of IFIs

A total of 298 febrile neutropenia episodes from 78 patients were evaluated retrospectively from the patient's medical records. Of the 298 febrile neutropenia episodes, 45 (15.1%) of them were related to IFIs according to the EORTC/MSG criteria. The distribution of IFI episodes was as follows.

Nine (3%) episodes were classified as proven, 8 (2.6%) as probable, and 28 (9.4%) as possible. Neutropenia was determined in 24 (77.4%) IFI episodes; profound neutropenia was detected in 18 (58%), and prolonged neutropenia was detected in 20 (64.5%). The median duration of neutropenia before IFI episode onset was 23 days (range, 3-103 d). IA accounted for the majority of IFI episodes; 77.7% (n = 35) were IA, 13.3% (n = 6) were invasive candidiasis (IC), and 8.8% (n = 4) were other rare fungal infections, respectively.

Proven IFI

During the study period, nine patients had nine proven IFI episodes. *Candida* spp. was the causative agent in 6 (66.6%) episodes; *C.albicans* was isolated in one (11.1%) episode and the remaining 5 episodes were caused by non-*albicans Candida* (55.5%) which were defined as central line-associated bloodstream infection; *C.glabrata* was isolated in

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TABLE 1. Comparison of Patients With IFI and Non-IFI

Characteristic	IFI (n = 28)	Non-IFI (n = 50)	*p*
Age, mo, median (IQR)	165.5 (135)	133.5 (134)	**0.04**
Sex, n (%)			
Male	14 (50)	26 (52)	0.52
Female	14 (50)	24 (48)	
Risk			
Standard risk	18 (64.3)	21 (42)	0.16
Medium risk	2 (7.1)	5 (10)	
High risk	8 (28.6)	24 (48)	
Relapse	14 (50)	11 (22.4)	**0.01**
Voriconazole prophylaxis	15 (53.6)	39 (78)	**0.01**
Mortality	14 (50)	14 (28)	0.08

The bold values indicate statistical analysis differences and correlations were considered significant at $P < 0.05$.

IFI indicates invasive fungal infection; IQR, interquartile range.

2 episodes, *C.albicans* in 1 episode, *C.parapsilosis* in 1 and *C.kefyr* (*Kluvyeromyces marxianus*) in 1 fungemia episode. Another proven IFI episode due to *Candida* spp. was considered in a patient with *C.glabrata* in pleural fluid. No proven IFI due to Aspergillosis was detected in our series.

Other rare fungal infections accounted for 33.3% (n = 3) of proven IFIs. In one patient *Acremonium* spp. was isolated from the lung by deep tissue cytopathology. *Geothricum capitatum* (*Blastoschizomyces capitatus*) was isolated from hemoculture in one patient, and one patient had *Trichosporon asahii* fungemia. The proven IFI episodes are summarized in Table 2.

Probable IFI

In the probable IFI group, 2 patients were diagnosed with bronchoalveolar lavage liquid (BAL) culture; *A. fumigatus* was isolated in one, and both *A.fumigatus* and *A.flavus* were isolated in the other patient. Direct microscopic examination of a specimen obtained by biopsy from the nasal septum revealed hyphae, and *A. flavus* was isolated from tissue culture in one patient who had resistant disease and died despite antifungal combinations. *Fusarium* spp. was documented in one patient who had a necrotic lesion in the nasal septum while receiving voriconazole prophylaxis. Four months after the first episode, *Candida glabrata* was isolated from the pleural fluid, and the patient died of pulmonary deterioration. He was the only patient with 2 IFI episodes and also relapse disease developed during this period.

The remaining 4 patients with findings suggesting lower respiratory tract infection, at least one finding compatible with fungal pneumonia on chest CT, and at least two positive serum GM antigenemia were defined as probable IFI. The risk factors for developing IFI are summarized in Table 3.

Antifungal Prophylaxis

Voriconazole prophylaxis was administered to n = 54 (69.2%) of the patients. IFI attack rate was compared within 2 periods regarding mold-effective prophylaxis; a significant decrease was achieved with voriconazole prophylaxis ($P = 0.01$, odds ratio [OR]: 0.288, 95% CI:0.104-0.797). Nineteen (6.3%) IA (proven/probable/possible) episode was determined in 10 patients before the pre-prophylaxis period, and 16 (5.3%) episodes in 12 patients were recorded after prophylaxis with voriconazole. A significant decrease was also achieved on CT findings suggestive of fungal

TABLE 2. Characteristics of the Patients With Proven IFI

Patient	Cause of proven infection	Infection site	Treatment	Outcome
HR, relapsed AML	*C.glabrata*	Blood (CLABSI)	Caspofungin	Death
HR, relapsed AML	*Acremonium spp.*	Lung, deep tissue cytopathology	Voriconazole,caspofungin, posaconazole	Death (death occurred with worsening of pulmonary findings)
HR, relapsed AML	*C.albicans*	Blood (fungaemia)	Caspofungin	Death (negative culture was obtained for fungi)
HR, relapsed AML	**Geotricum capitatum*	Blood (CLABSI)	L-AMB	Death (*Acinetobacter* spp. bacteremia was detected 2 d before death
HR	*Trichosporon asahii*	Blood (fungaemia)	L-AMB	Survived
HR	*C.glabrata*	Blood (CLABSI)	L-AMB	Survived
HR, relapsed AML	*C.parapsilosis*	Blood (CLABSI)	caspofungin	Death (death occurred due to *Klebsiella* spp sepsis, 1 mo after a negative culture was obtained for fungi
HR, relapsed AML	*C.glabrata*	pleural puncture fluid	caspofungin	Death with pulmonary deterioration
HR, relapsed AML	†*C.kefyr*	Blood (CLABSI)	L-AMB, caspofungin	Death (death occurred due to *Pseudomonas* spp. sepsis, 6 mo after obtaining a negative culture for fungi)

*Geothricum capitatum renamed as Blastoschizomyces capitatus.
†C.kefyr renamed as Kluvyeromyces marxianus.
AML, acute myeloid leukemia; C, Candida; CLABSI, Central Line-associated Bloodstream Infection; HR, high risk; IFI, invasive fungal infection; L-AMB, liposomal amphotericin B.

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TABLE 3. Comparison of Cases in Terms of IFI Risk Factors

	Proven/probable IFI	Possible IFI	*p*	OR (95% CI)
Age at the diagnosis of IFI mo, median (range)	178 (8-219)	180 (16-234)	0.98	1.000 (0.987-1.013)
ANC/mm3 at the diagnosis of IFI median (range)	30 (0-1070)	195 (0-1290)	0.51	0.999 (0.997-1.002)
Duration of neutropenia episode days,median(range)	27 (7-103)	22 (3-63)	0.39	1.022 (0.972-1.074)
Prolonged neutropenia, n (%)	10 (50)	7 (46.7)	0.56	0.544 (0.069-4.270)
Relapsed AML, n (%)	14 (63.6)	3 (23.1)	**0.02**	0.152 (0.029-0.791)

AML indicates acute myeloid leukemia; ANC, absolute neutrophil count; IFI, invasive fungal infection; OR, odds ratio.

pneumonia with voriconazole prophylaxis ($P = 0.005$, OR:0.190, 95% CI:0.058-0.627). Although the IA incidence was decreased the difference was not statistically significant ($P = 0.05$). However, there was no significant change in the IFI rate due to *Candida* spp. with voriconazole prophylaxis. ($P > 0.05$). The effect of voriconazole prophylaxis is summarized in Table 4.

Antifungal Treatment

Empirical antifungal therapy was started in all patients with suspected IFI. Of all the IFI episodes, 13 were defined as proven, and 4 were as probable. In these episodes, 6 were treated with caspofungin alone, 6 with L-AMB alone, and only 1 with voriconazole alone. Antifungal combination therapy was used in 4 episodes; voriconazole and caspofungin in one, L-AMB and voriconazole in 3 episodes. There were 28 attacks considered as possible IA; it was determined that caspofungin was the first choice in these patients, but caspofungin and voriconazole combined treatment was used in 20 of them.

Mortality

Overall mortality in the study population was 35.8% (28/78). 4(5.1%) patients died due to complications of HSCT, 5(6.4%) patients died due to sepsis, and 19(24.3%) patients died due to resistant-refractory disease. There were 16 patients with proven and/or probable IFI, and the IFI-attributable mortality rate was 25% (4/16).

Risk factors affecting mortality in 78 children with AML were investigated. On univariate analysis, relapsed AML ($P = 0.000$) significantly increased the mortality rate. Sex, age at the diagnosis, presence of proven or probable IFI episode, and prolonged or profound neutropenia did not have a significant effect on the mortality rate ($P > 0.05$). On the multivariate analysis, independent risk factors for mortality were evaluated; relapsed AML ($P = 0.006$, OR:4.745) was the most significant risk factor for mortality (Table 5).

DISCUSSION

We present a study examining the incidence, epidemiology, and outcome of IFIs in pediatric AML patients, covering the period before and after prophylaxis with voriconazole. The incidence of IFIs was 15.1%; proven and probable IFIs accounted for 5.1%. Various IFI rates have been reported in many studies among patients with ALL and AML or concomitant solid tumors. Kazakou et al[13,14] retrospectively investigated the incidence of IFIs in a pediatric hematology-oncology department, and the crude incidence rate of IFIs in ALL and AML were 10.5%, and 18.2%, respectively. An Australian multicentre 10-year review determined the overall prevalence as 20.7% for proven/probable/possible IFIs, and 10.3% in pediatric AML patients.[14] The incidence of IFIs was reported to be 20.5% in pediatric patients with AML from Taiwan.[12] Similar to our study involving only pediatric AML patients, IFI was demonstrated in 12% of the patients in a recent study which was lower than ours which can be explained by patients' heterogeneity.[2] Sezgin et al[6] evaluated the IFIs in childhood leukemia and reported that 39.4% of the patients developed IFIs; however, the study included both ALL and AML patients.

Many previous publications mentioned that IA and *Candida* spp. are responsible for most of the episodes of IFI that develop in pediatric AML patients. Sung et al[15] documented similar rates of *Aspergillus*(31%) and *Candida* spp. (24.9%) in infection-related mortality reports in children with AML. Lehrnbecher et al[9] reported that *Aspergillus* accounted for 66.7% and *Candida* for 33.3% and thus, they suggested that *Aspergillus* is the prominent pathogen in pediatric AML. Among pathogens implicated in proven/probable IFD episodes, 74.4% were molds, and over one of three (37.9%) were non-*Aspergillus* spp. in a recent study.[14]

Candida spp. was the most common pathogen (46.1%) in proven IFI episodes, and the predominance of non-albicans Candida (38.4%) was remarkable in our study which may be explained by the fact that all patients had indwelling long-term central venous catheters. Lin et al[12] reported that *Candida* species caused the majority (59.1%) of IFIs similar to our study. Johnston et al[2] determined that *Candida* species accounted for 50% and *Aspergillus* spp. accounted for 30.4%. of IFIs. The rate of IA in the proven IFI group may be unrealistic because, in many patients, invasive diagnostic procedures could not be performed, and the necessary tissue samples could not be obtained because of the poor clinical condition of the patients. The significant decrease in the rate of total IFI episodes, IA episodes, and fungal pneumonia on

TABLE 4. Comparison of Patients in Terms of Voriconazole Prophylaxis

	No prophylaxis (n = 24)	Voriconazole prophylaxis (n = 54)	*p*	OR (95% CI)
IFI episode (n [%])	13 (56.5)	15 (27.3)	**0.01**	0.288 (0.104-0.797)
IA episode (n [%]) *(Proven, probable, possible)*	10 (56.5)	12 (21.8)	0.05	
IFI due to *Candida* spp. (n [%])	4 (17.4)	5 (9.1)	0.2	
Fungal pneumonia on CT scan (n [%])	9 (39.1)	6 (10.9)	**0.005**	0.190 (0.058-0.627)

CT indicates computerized tomography; IA, invasive Aspergillozis; IFI, invasive fungal infection; OR, odds ratio.

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TABLE 5. Risk Factors for Mortality According to Multivariate Analysis

Risk factor	*p*	Odds ratio	95% CI
Age at the diagnosis	0.49	0.997	0.987-1.006
High-risk AML	**0.01**	0.255	0.087-0.744
Relapse	**0.006**	4.745	1.573-14.316
IFI episode	0.12	2.125	0.822-5.493
Profound neutropenia	0.65	1.494	0.260-8.594
Prolonged neutropenia	0.51	1.734	0.328-9.157

AML indicates Acute myeloid leukemia; IFI, invasive fungal infection.

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CT with mold-active prophylaxis with voriconazole may also support this view. Moreover, an increased rate of yeast-related episodes or invasive zygomycosis after mold-active antifungal prophylaxis was not observed.

Prolonged and profound neutropenia, chemotherapy of high-intensity, resistant disease, TPN infusion, broad-spectrum antibiotics, and corticosteroids are among the most frequently emphasized risk factors for IFIs.[2,16] Relapse disease was the most significant risk factor, whereas neutropenia and its duration did not alter as expected for proven/probable IFIs compared with possible IFIs in our study. Besides, patients in the IFI group were older than those who did not develop IFIs. Similarly, some studies demonstrated that older age was a risk factor for IFIs in pediatric patients with a hematology-oncology disease or undergoing HSCT.[8,17] The increase in host colonization by environmental fungi with age may cause this condition.

Previous studies including other cancer patients, not only AML patients reported mortalities of 21.3% to 63.6%.[1,18–20] Kobayashi et al[8] reported 48.2% of IFI-related mortality, which was much higher in patients with lung lesions in children with hematologic and malignant diseases. The overall mortality was 35.8% in our series, and attributable mortality occurred in 4 patients who died from the direct cause of IFI. Another study involving only pediatric AML patients determined the overall mortality of IFIs as 53%; patients with pulmonary Aspergillosis had the highest mortality and the IFI-attributable mortality was 27.4%, similar to our study.[12] Independent risk factors affecting mortality were reported as relapsed/ refractory AML, development of an IFI episode especially invasive mold infections, and pulmonary Aspergillosis in recent articles.[6,8] The relapsed AML was the most significant risk factor associated with mortality, and the development of an IFI episode had no significant effect on the mortality in our study. This result may be explained by the fact that 24.3% of the patients died due to resistant-refractory disease, by the rapid initiation of antifungal treatment in case of clinical suspicion and the application of mold-effective antifungal prophylaxis with voriconazole, which has been standardized for a long time in our clinic.

The retrospective nature, reflecting a single-center experience, and the small number of cases are among the limitations of our study. Although it seems like a limitation to include only AML patients, our study may contribute to the literature due to the limited data on IFIs in these patients and the experience of the center where mold-active antifungal prophylaxis was administered.

In conclusion, we determined 15.1% of the febrile neutropenia episodes were related to IFIs. In the whole group (proven/probable/possible), IA accounted for the majority of IFI episodes, whereas non-*albicans Candida* was the most frequently detected pathogen in the proven IFI group. Relapsed AML was the most significant risk factor associated with IFIs, and relapsed AML increased mortality due to IFIs. Mold-active prophylaxis with voriconazole significantly decreased the rate of IFIs and IA episodes. However, the current results revealed that IFI-related mortality could be high as 25%, and one of every four patients could die if the patient can not be prevented from IFI. Further investigations should be conducted to identify risk factors affecting IFI-related mortality and to improve the poor outcome of these patients.

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