



Original Article

Invasive Fungal Diseases in Children with Acute Leukemia and Severe Aplastic Anemia

Sutatta Supatharawanich¹, Nattee Narkbunnam¹, Nassawee Vathana¹, Chayamon Takpradit¹, Kamon Phuakpet¹, Bunchoo Pongtanakul¹, Sasima Tongchai², Phakati Sinlapamongkolkul³, Popchai Ngamskulrungraj⁴, Wanatpreeya Phongsamart⁵, Kleebsabai Sanpakit¹ and Jassada Buaboonnam¹.

¹ Division of Hematology and Oncology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

² Office for Research and Development, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

³ Department of Pediatrics, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand.

⁴ Department of Microbiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

⁵ Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

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Abstract. Although the outcomes of childhood leukemia and severe aplastic anemia (SAA) have improved, infectious complications are still the major concern. Particularly worrisome are invasive fungal diseases (IFDs), one of the most common causes of infectious-related deaths in patients with prolonged neutropenia. A retrospective study was conducted of IFDs in pediatric patients with newly diagnosed or relapsed acute leukemia, or with SAA, at Siriraj Hospital, Mahidol University, Thailand. There were 241 patients: 150 with acute lymphoblastic leukemia (ALL), 35 with acute myeloid leukemia (AML), 31 with relapsed leukemia, and 25 with SAA. Their median age was 5.4 years (range, 0.3–16.0 years). The overall IFD prevalence was 10.7%, with a breakdown in the ALL, AML, relapsed leukemia, and SAA patients of 8%, 11.4%, 19.3%, and 16%, respectively. Pulmonary IFD caused by invasive aspergillosis was the most common, accounting for 38.5% of all infection sites. Candidemia was present in 34.6% of the IFD patients; *Candida tropicalis* was the most common organism. The overall case-fatality rate was 38.5%, with the highest rate found in relapsed leukemia (75%). The incidences of IFDs in patients with relapsed leukemia and SAA who received fungal prophylaxis were significantly lower than in those who did not ($P = N/A$ and 0.04, respectively). IFDs in Thai children with hematological diseases appeared to be prevalent, with a high fatality rate. The usage of antifungal prophylaxes should be considered for patients with SAA to prevent IFDs.

Keywords: Aplastic anemia; *Candida*; Fungal infection; Leukemia.

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Correspondence to: Jassada Buaboonnam, MD, Associate Professor of Pediatrics Division of Hematology and Oncology, Department of Pediatrics Faculty of Medicine, Siriraj Hospital, Mahidol University 2 Wanglang Road, Bangkok Noi Bangkok 10700, Thailand. Tel:+66 2 419 5971. Fax: +66 2 866 3021 E-mail: onco008@yahoo.com

Introduction. The outcomes of pediatric leukemia have drastically improved over the past decade, with 5-year overall survival (OS) rates of 80%–90%^{1,2} and 70%^{3,4} for acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), respectively. However, owing to prolonged neutropenia secondary to chemotherapy, infectious complications such as invasive fungal diseases (IFDs) may occur and become a significant cause of death in such patients, particularly in cases of AML.^{5,6} Apart from directly causing morbidity and mortality, IFDs might delay the treatment of leukemia and ultimately have an impact on disease-free survival. Likewise, other diseases manifesting with prolonged neutropenia, such as severe aplastic anemia (SAA), might be at risk of IFDs. The incidence of IFDs in children has been reported to vary with the underlying disease, ranging from 8.4% to 20% in AML and from 10% to 11% in ALL,⁷⁻⁹ whereas the IFD incidence of SAA in both children and adults is between 8% and 21%.^{10,11} Apart from pre-existing disease, environmental factors (such as the construction of the hospital) and changes in clinical practice (such as the use of antibiotic prophylaxis) may be risk factors for IFDs. These may cause variations in IFD rates between countries.¹² However, there are scarce data on the incidence and outcomes of IFDs in Thai children with leukemia and SAA. Investigation of these two aspects in such patients may guide physicians in preventing IFDs and improving IFD treatment. The current research aimed to retrospectively study the prevalence and outcomes of IFDs in pediatric leukemia and SAA and to determine the risk factors for IFDs in such patients.

Patients and Methods. A retrospective review was conducted on all children aged younger than 16 years, diagnosed with ALL, AML, and SAA between 2009 and 2019 at Siriraj Hospital, Mahidol University. The demographic data collected comprised sex, age, diagnosis of disease, and risk classification. The clinical factors analyzed were the presence of central venous line, the duration of neutropenia, the genetic polymorphism of *TPMT* and *NUDT15* (only for ALL), diagnosis of IFD, antifungal prophylaxis, antifungal treatment, and organ involvement.

The ALL and AML diagnoses were established by cell morphology, flow cytometry, and cytogenetics, while SAA diagnoses were based on Camitta's criteria.¹³ Cytogenetics and chromosomal breakage studies were done to exclude congenital bone marrow syndrome. The incidences of IFDs during the conditioning regimen and after allogeneic stem cell transplantation were excluded.

Antifungal prophylaxis (AFP) was not routinely prescribed for patients with ALL, except for those treated with infant or relapsed protocol. Patients with AML diagnosed before 2014 received AFP at physician discretion, whereas all patients diagnosed after 2014

received AFP according to the consensus of the Thai Pediatric Oncology Group 2016 guidelines.¹⁴ The SAA patients received AFP at physician discretion; after 2017, all SAA patients received AFP since an institute guideline had been implemented. Itraconazole (ITRA) solution or fluconazole was deemed the first-line AFP, whereas posaconazole suspension was considered as an alternative for those aged > 13 years. Therapeutic drug monitoring was performed for those receiving posaconazole suspension and ITRA to maintain a trough serum of more than 0.7 mcg/ml and 0.5–4 mcg/ml, respectively. The diagnoses of IFD were categorized as “proven”, “probable”, and “possible”, using the criteria of the Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group.¹⁵ Our research was approved by the Ethics Committee of the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si299/2562).

Descriptive statistics were used to detail the demographic and clinical characteristic data. Medians and ranges were calculated for continuous data, while numbers and percentages were used to describe categorical data. Pearson's chi-squared test, Yates' continuity correction, or Fisher's exact test was used to compare the proportions between groups for categorical data, and the Mann–Whitney U test was used to compare medians for continuous data. To check for normal distribution of data, the Shapiro–Wilk test was performed. Simple and multiple binary logistic regression analyses were used to assess factors associated with IFDs. The magnitude and direction of association between the factors and the IFDs were identified using odds ratio (OR) with 95% confidence interval (95% CI). A P value < 0.05 was considered statistically significant. All analyses were performed using PASW Statistics for Windows (version 18.0; SPSS Inc., Chicago, IL, USA).

Results. In all, 241 patients were enrolled. Their median age at diagnosis of hematological disease was 5.4 years (range, 0.3–16.0). The patient and clinical characteristics data are detailed in **Table 1**. Probable and proven IFDs were diagnosed in 26 patients, whereas possible IFDs were diagnosed in 27. The overall IFD prevalence was 10.7%. The median duration of neutropenia before the diagnosis was 18.5 days (range, 0 to 121). The prevalences of IFDs in the ALL, AML, relapsed leukemia, and SAA patients were 8%, 11.4%, 19.3%, and 16%, respectively. Of all IFDs in both ALL and AML, most were diagnosed during the induction phase (11 patients [91.7%] and two patients [50%], respectively).

Of all the IFD patients, proven IFD and probable IFDs were found in 13 (50%) and 13 (50%), respectively.

Table 1. Patient and clinical characteristics of pediatrics with hematological diseases.

Characteristic	Total (n = 241)	IFD (n = 26)	Non-IFD (n = 215)	P value
Age (yr)				
Median (min, max)	5.4 (0.3, 16.0)	6.8 (1.3, 15.1)	5.2 (0.3, 16.0)	.233
Sex, n (%)				
Male	127 (52.7)	15 (57.7)	112 (52.1)	.589
Female	114 (47.3)	11 (42.3)	103 (47.9)	
Underlying disease, n (%)				
ALL	150 (62.2)	12 (46.2)	138 (64.2)	.231
AML	35 (14.5)	4 (15.4)	31 (14.4)	
Relapsed leukemia	31 (12.9)	6 (23.0)	25 (11.6)	
SAA	25 (10.4)	4 (15.4)	21 (9.8)	
Antifungal prophylaxis, n (%)				
Yes	49 (20.3)	4 (15.4)	45 (20.9)	.685
No	192 (79.7)	22 (84.6)	170 (79.1)	
Drug, n (%)				
Itraconazole	25 (51.0)	2 (50.0)	23 (51.1)	.211
Fluconazole	14 (28.6)	0 (0)	14 (31.1)	
Posaconazole	10 (20.4)	2 (50.0)	8 (17.8)	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; IFD, invasive fungal disease; SAA, severe aplastic anemia.

Table 2. Identifiable organisms and sites of infection.

	ALL and infantile ALL (n = 12)	AML (n = 4)	Relapse leukemia (n = 6)	SAA (n = 4)	Total
IFI diagnosis, n)%(
Proven	6 (50.0)	3 (75.0)	3 (50.0)	1 (25.0)	13 (50.0)
Probable	6 (50.0)	1 (25.0)	3 (50.0)	3 (75.0)	13 (50.0)
Primary source of infection, n)%(
Lung	5 (41.7)	1 (25.0)	3 (50.0)	1 (25.0)	10 (38.5)
Aspergillus spp	5	1	3	1	
Hepatosplenic	2 (16.7)	1 (25.0)	1 (16.7)		4 (15.4)
<i>C. tropicalis</i>	1		1		
<i>C. glabrata</i>		1			
<i>Candida</i> spp	1				
Paranasal sinus	1 (8.3)			2 (50.0)	3 (11.5)
Aspergillus spp				1	
Mucormycosis					
Fungemia	4 (33.3)	2 (50.0)	2 (33.3)	1 (25.0)	9 (34.6)
<i>C. tropicalis</i>		1	2		
<i>C. albicans</i>		1			
<i>C. krusei</i>				1	
Duration of neutropenia prior to diagnosis of IFD (days)					
Median	12.0	13.0	16.5	73.0	16.0
(min, max)	(0, 23.0)	(5, 21.0)	(5.0, 34.0)	(40.0, 121.0)	(0, 121.0)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; IFD, invasive fungal disease; SAA, severe aplastic anemia.

Among those with invasive candidiasis, *Candida tropicalis* was the most commonly identified organism. **Table 2** lists the identified organisms and their sites of infection. Ten patients (38.5%) had pulmonary IFD, nine (34.8%) had fungemia, four (15.4%) had hepatosplenic IFD, and three (11.5%) had paranasal sinus IFD. All ten patients with pulmonary IFD were diagnosed with invasive pulmonary aspergillosis (IPA). Of all 27 possible IFD patients, twenty-six were provisionally diagnosed with pulmonary IFD with the negativity of serum galactomannan; one patient had hepatosplenic IFD without mycological evidence.

Antifungal treatment was prescribed for all 26 IFD patients, whereas 5 patients received combined medical and surgical intervention. The overall case-fatality rate of those with IFDs was 38.5%. The case-fatality rates for ALL, AML, relapsed leukemia, and SAA patients were 8.3%, 25.0%, 83.3%, and 75.0%, respectively.

With regard to the ALL patients, the NCI risk classification, the presence of central venous line, and *NUDT 15* and *TPMT* polymorphisms were not factors associated with their IFDs. As to the AML patients, Down syndrome, central venous line, and prolonged neutropenia of more than one month were not associated

Table 3. The prescribed antifungal prophylaxes of pediatrics with hematological diseases.

Disease	Antifungal prophylaxis	IFD (n = 4)	Non-IFD (n = 45)	Total (n = 49)	P value
ALL	Itraconazole	1 (50.0)	4 (100)	5 (83.3)	0.333
	Posaconazole	1 (50.0)	0	1 (16.7)	
AML	Itraconazole	1 (100)	8 (61.5)	9 (64.3)	0.741
	Fluconazole	0	2 (15.4)	2 (14.3)	
	Posaconazole	0	3 (23.1)	3 (21.4)	
Relapsed leukemia	Itraconazole	0	8 (53.3)	8 (53.3)	N/A
	Fluconazole	0	3 (20.0)	3 (20.0)	
	Posaconazole	0	4 (26.7)	4 (26.7)	
SAA	Itraconazole	0	3 (23.1)	3 (21.4)	0.040
	Fluconazole	0	9 (69.2)	9 (64.3)	
	Posaconazole	1 (100)	1 (7.7)	2 (14.3)	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; IFD, invasive fungal disease; N/A, not applicable; SAA, severe aplastic anemia.

with the IFDs. In the aplastic anemia group, ANC < 200/mm³ and duration of treatment of more than three months were not associated with the IFDs. The independent factors associated with IFDs for patients with proven IFD, probable IFD, and possible IFD are presented in **Supplemental Table 1**.

The types of AFP are summarized in **Table 3**. ITRA was the most commonly prescribed AFP for patients with ALL, AML, and relapsed leukemia (62.8%); fluconazole was the most common for patients with SAA (64%). The median duration of fungal prophylaxis was 158 days, ranging from 10 days to 1,102 days. As to relapsed leukemia and SAA, the IFD prevalence of patients receiving AFP was significantly lower than that for those who were not administered an AFP (P = N/A and 0.04, respectively). With ALL and AML, the IFD prevalences of the two groups were not significantly different (P = 0.33 and 0.74, respectively).

Discussion. In the present study, the prevalences of IFDs in pediatric ALL and AML patients (8% and 11.4%, respectively) were higher than the values reported by other pediatric studies, especially those conducted in nontemperate zone countries.^{5,16} Environmental and geographical factors might be plausible causes leading to the increased incidence of IFDs in tropical countries.¹⁷ Antifungal prophylaxis practice also affects IFD prevalence. Furthermore, the current work found that the prevalence in individuals with relapsed leukemia was higher than in non-relapsed patients. Prolonged exposure to myelotoxic agents causing prolonged immunosuppression in both humoral- and cell-mediated immunity may heighten the risk of IFDs in relapsed patients.^{18,19} In our study, the occurrence of IFDs was common during the initial treatment of both the ALL and

AML patients. Therefore, clinical suspicion of an IFD should be taken into consideration even if patients have initially received induction therapy. The prevalence of IFDs in pediatric SAA patients has been reported to range between 8% and 22%,^{20,21} whereas that in adult SAA patients in Thailand was 21.2%,¹¹ compared with 8% in nontemperate countries.²² Likewise, the reasons mentioned above might plausibly explain the higher incidence of IFDs (approximately 16%) revealed by our investigation. This finding may highlight the role of IFD prophylaxis for SAA patients.

Candida infections were the most frequently identifiable cause of the IFDs in this study, which is concordant with other published pediatric studies.²³ *C. tropicalis* was the most common pathogen in the present work. This species appears to be prevalent in Asia, particularly in the tropical regions of Asia, such as India and Thailand.^{24,25} In contrast, *C. albicans* has been reported to be the most common organism in most parts of Southwest Asia^{26,27} and non-Asian regions.^{28,29} Research has also found that the incidences of azole-resistant strains of *C. tropicalis* have increased,³⁰ and that the azole resistance of *C. tropicalis* is approximately ten times that of *C. albicans* (20.8% vs. 2.3%).^{31,32} Hence, conducting a sensitivity test may play a pivotal role in determining the appropriate treatment for patients.

IPA was the most common IFD in our study, and that corresponds with the trends of increasing incidence rates observed by other investigations.^{23,33} Our work found that IPA accounted for 16% of the IFD cases, and that may underscore the roles of clinical and radiographical monitoring as well as serum galactomannan testing in individuals with a suspected IFD. The proportion of possible IFDs in the current investigation was 50.9%; most of those cases had the clinical manifestations of a

pulmonary infection in the absence of mycological criteria. Since the sensitivity of the serum galactomannan test is 70%,³⁴ the true prevalence of the IFDs-especially pulmonary IFD-in our study might be higher than we have reported. Further investigation might be warranted to improve the diagnostic yield for such cases.

Among the SAA patients of the present study, the proportion of cases with mold infections was higher than of those with candida infections, and that is in accord with the prevalence rates found in adult studies;^{10,11} data for children are scarce. Although recent guidelines recommend using antimold azole or echinocandin for AML, relapsed leukemia, and high-risk ALL,³⁵ there are currently no recommendations for using an AFP for the treatment of SAA. In our study, the IFD incidence in SAA was high; however, the incidence for the SAA patients given an AFP was significantly lower than that for the patients without an AFP. Therefore, it is recommended that the usage of an AFP with antimold activity, such as ITRA, should be expanded to include patients with SAA, especially in a tropical country such as Thailand.

The reported case-fatality rates of IFDs in children with hematological malignancies have varied between 20% and 50%, with the prevalences appearing to depend upon the site of involvement, pre-existing disease, and organism type.^{8,36,37} Although the current work demonstrated case-fatality rates of 15% to 30% for newly diagnosed leukemia and SAA patients, the mortality was as high as 90% for the relapsed leukemia patients. Host factors (severe immunocompromised status, prolonged antimicrobial use, and severe damage of the mucosal membrane) may exacerbate the risk of IFDs in cases of relapse. Thus, individuals with relapsed leukemia who are clinically suspected of an IFD may need early and intensive treatment to prevent morbidity and mortality.

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Other clinical factors have been reported to present a risk of IFDs, such as NCI risk classification, the presence of Down syndrome,³⁸ the usage of a central venous catheter,³⁹ and the duration of neutropenia.⁴⁰ The genetic polymorphism of genes involving thiopurine metabolism, such as *NUDT15*, is associated with an increased risk of infection in ALL patients.⁴¹ In our investigation, the aforementioned clinical factors were not statistically associated with IFDs. Our univariate analysis found that when possible IFDs were included, age at diagnosis of > 4 years, relapsed leukemia, AML, and SAA were independent risk factors for IFDs. In our subsequent multivariate analysis, very severe aplastic anemia (ANC < 200 mm³) was associated with an increased risk of IFDs. Therefore, patients with very severe aplastic anemia should be made aware of the possibility of developing an IFD, and an AFP should be initiated while the diagnosis is being established.

This study had limitations that need to be mentioned. Firstly, given the nature of retrospective studies, there might be a risk of missing or incomplete data. Secondly, the pediatric population in this study was drawn from a national tertiary referral hospital; therefore, the data may not be fully generalized to other populations.

Conclusions. The prevalence of IFDs in Thailand appeared higher than the rates reported for other countries. The usage of an AFP should be considered to prevent mortality in SAA patients as well as AML and relapsed leukemia patients.

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Supplementary Data:

Supplemental Table 1. Independent factors of IFD.

Factors	Crude OR (95% CI)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> value
Underlying disease				
ALL	Reference			
AML	4.074 (1.763–9.415)	.001**	4.121 (1.611–10.544)	.003**
SAA	4.596 (1.807–11.693)	.001**	3.653 (1.186–11.255)	.024**
Relapsed leukemia	5.678 (2.414–13.358)	< .001**	5.124 (1.919–13.680)	.001**
Antifungal prophylaxis	2.609 (1.377–4.943)	.003**	0.976 (0.424–2.246)	.954
Age of diagnosis > 4 years	2.944 (1.431–6.056)	.003**	2.271 (1.050–4.911)	.037*

*, **, significant at .05 and .01 levels, respectively

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; SAA, severe aplastic anemia