Role of Antifungal Prophylaxis in Invasive Fungal Infection in Children with Acute Lymphoblastic Leukemia—A Retrospective Cross-Sectional Study

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Ind J Med Paediatr Oncol 2022;43:491–499.

Abstract

Introduction Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Its outcome in India is not as good as that in the western world. One of the important reasons for lesser survival rates is opportunistic infections, including invasive fungal infections (IFIs). Antifungal prophylaxis (AFP) in ALL children is routinely not followed. However, owing to its incidence in high-risk ALL, this study is focused on the use of AFP in those children.

Objectives This retrospective study investigated the role of AFP in newly diagnosed children with high-risk ALL on intensive blocks of therapy on regimens B and C of the United Kingdom Acute Lymphoblastic Leukemia 2003 protocol.

Materials and Methods The study was conducted in a tertiary care center from 1st December 2013 to 31st December 2019 and included children with ALL from 1 to 18 years of age. Routine AFP with voriconazole was commenced for high-risk ALL children from 1st July 2017 onward in our center. We analyzed data of all IFIs in children before and after AFP with National Cancer Institute high-risk status who had been started on regimen B induction and regimen B or C consolidation and intensification phases.

Results A total of 55 children with high-risk ALL were included in the study. The median age was 4 years, with the majority being between the age of 1 and 10 years (38 out of 55; 65%) and predominantly male (36 out of 55; 69%). Total incidence of IFI in our cohort was 51% (28 out of 55). A significant number of children (16 out of 22 [70%]) who were not on prophylaxis developed IFI versus children (12 out of 33 [28%]) on prophylaxis ($p = 0.008$). The most common organisms isolated were *Candida parapsilosis* and *Candida tropicalis.* Children not receiving AFP were found to be 4.7 times (95% confidence interval: 1.44–15.13) more likely to get IFI than the ones receiving AFP. The presence of concurrent bacterial infection increases the risk of IFI ($p = 0.04$).

Conclusion The incidence of IFI was high in high-risk ALL children who were not on AFP. The introduction of routine AFP reduced the incidence of IFI.

Keywords
- Acute lymphoblastic leukemia
- fungal infection
- childhood cancer

DOI https://doi.org/10.1055/s-0042-1756480.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy worldwide, accounting for more than 25% of all pediatric cancers.[1] Pediatric ALL is often cited as one of the true success stories of modern medicine.[2] The United Kingdom Acute Lymphoblastic Leukemia (UKALL) 2003 trial[3,4] results have shown an overall outcome of 90% in the United Kingdom.[3] Its event-free survival rate at 3 years in India has been observed, ranging from 41to 85% across the country.[5,6]

Children undergoing the treatment for cancers are at an increased risk of developing invasive fungal infections (IFIs). IFIs pose a significant challenge to the management of ALL as it results in morbidity, mortality, and interruption of treatment. Incidence of IFI was found to be high in children with acute myeloid leukemia (AML) (up to 29%), allogeneic hematopoietic stem cell transplantation (HSCT), and relapsed ALL.[7] The overall case fatality rate is about 20 to 70%, with the most inferior outcome noted with disseminated disease. *Candida* species was the most common organism isolated, followed by *Aspergillus*. Recently, Zygomycetes, *Fusarium spp*., and *Sedoporium spp.* are being increasingly observed in IFI cases.[8,9] The fungal microflora present in our set-up, primarily consisted of *Candida parapsilosis* and *Candida tropicalis*, both of which are fluconazole resistant. Also, we wanted to target molds which remain the most common etiology for IFIs in immunocompromised patients, that is, here, ALL children. Because of these two reasons, voriconazole was chosen as antifungal prophylaxis (AFP) of choice and the antifungal policy was gradually adjusted in our medical center.

Incidence of IFI is comparatively less common during the treatment for newly diagnosed ALL than in AML/relapsed ALL/HSCT cases, and it varies depending on the protocol, regimen followed, and risk factors involved. However, there are no standard guidelines for commencing AFP in children receiving the treatment for ALL. The analysis of infection-related mortality in the UKALL 2003 protocol[10] showed that 20% of patients had a fungal infection (predominantly *Aspergillus*), and it was common during the induction phase of the treatment. It is the second most common cause of infection-related mortality in ALL children. Hence, we investigated the role of AFP in children with ALL to improve the quality of life and reduce treatment-related morbidity and mortality.

Objectives

This study was to investigate the role of AFP in newly diagnosed ALL children who had National Cancer Institute (NCI) high-risk status during the intensive phases of regimens B and C, as per UKALL 2003 protocol.

Methodology

Study Population

It was a retrospective study. All children aged consecutively between the age of 1 and 18 years diagnosed with ALL who had NCI[11] high-risk status (initial white blood cells [WBC] count $\geq$50,000/mm^3 or age $\geq$10 years or T cell type) between 1st December 2013 and 31st December 2019 admitted and treated at our tertiary care center, Kasturba Medical College and Hospital, Mangalore, were included. All the details of children with the type of leukemia (B or T cell), age at diagnosis, date of initiation of treatment, regimen, post-induction medical residual disease status, details about febrile neutropenia episodes, event dates (relapse and death) during the induction, consolidation, interim maintenance or escalating Capizzi, and delayed intensification blocks were obtained using structured proforma through review of medical records. All these pieces of information were obtained after due permission from the Medical Records Section of the hospital. Children on regimen A, aged less than 1 year or more than 18 years, relapse/recurrent cases, and IFIs in the maintenance phase of treatment were all excluded from our study.

Invasive Fungal Infection Prophylaxis

In our unit, AFP was started as per routine practice on 1st July 2017 for those children receiving treatment on regimens B and C of the UKALL 2003 protocol. The prophylaxis was based on the observation of presumed increased incidence of IFI in our cohort of children with ALL. Hence, the study population was divided into two groups, the first group included the children diagnosed before 1st July 2017 and not on AFP and the second group included children diagnosed after 1st July 2017 and on AFP. The antifungal prophylactic agent used was oral voriconazole (dose ranging between 6 to 10 mg/kg/dose) twice daily, and for those who cannot take the drug orally or due to financial constraints, these children received intravenous (IV) conventional amphotericin B (1 mg/kg/d) on alternate days. While receiving amphotericin B, creatinine and potassium levels were monitored twice weekly. Due to the culture pattern in our set-up being fluconazole resistant as well to target molds, voriconazole was chosen as our AFP of choice and the antifungal policy was gradually adjusted. Itraconazole (5 mg/kg/d in two divided doses) and fluconazole (12 mg/kg/dose once-daily dosing) were used as AFP before the introduction of voriconazole in 2017. Unfortunately, therapeutic drug monitoring for voriconazole was not performed on our patients due to the nonavailability of the facility.

Treatment Regimen for Underlying Leukemia

ALL was diagnosed based on bone marrow examination showing blast cells $\geq$20% and confirmed through flow cytometry.[12] All the children with ALL were treated on the uniform protocol mentioned in UKALL 2003 as outlined in ►**Fig. 1**.

Treatment for Invasive Fungal Infection

For all children who developed fever, before the initiation of broad-spectrum antibiotics, tests such as blood culture and complete blood count were performed along with urine culture performed in children <5 years and girls of all ages. As per the guidelines, we started amphotericin B (1 mg/kg/d, conventional drug given through IV) in children

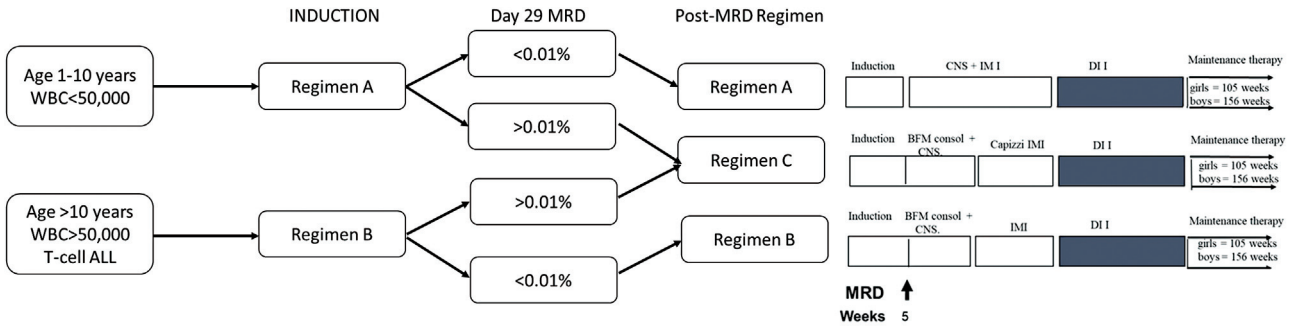

Fig. 1 UKALL 03 treatment regimens. BFM, Berlin–Franklin–Munster consolidation; IM, interim maintenance; DI, delayed intensification; MRD, minimal residual disease.

with persistent fever spikes and neutropenia ($<500/mm^3$) lasting more than 96 hours after starting antibiotics with negative bacterial cultures. If suspicion of IFI was raised, based on prolonged fever and negative cultures, chest X-ray and abdominal ultrasonography were performed in all children. Serum galactomannan levels were analyzed using Platelia Aspergillus Ag enzyme-linked immunosorbent assay kit, and cerebrospinal fluid analysis and culture, computed tomography (CT) chest/sinus, echocardiography, and other imaging studies were performed on a case-to-case basis. IFI was classified according to the European Organization of Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) guidelines.[13]

Sample Size and Outcome Measures

This was a time-bound study analyzing all the ALL diagnosed children admitted during the study period and including only those satisfying the inclusion criteria. The primary outcome of the study was to identify and classify fungal infections and to assess the role of AFP in preventing them. The secondary outcome measure was to identify the relevant risk factors contributing to the fungal infection.

Ethics

The study was approved by the Institute's Ethics Committee (IEC KMC MLR 02-2021/71), and all the patients consented to the collection and analysis of the data. Kasturba Medical College Hospital, Mangalore, is a tertiary-level teaching hospital that has a dedicated Division of Pediatric Oncology under the Department of Pediatrics. Written informed consent was waived off due to the retrospective nature of the study. No harm was done to the study participants, and all the ethical principles under the Declaration of Helsinki were met.

Definitions

Febrile Neutropenia

A single spike of fever >38°C or 100°F with an absolute neutrophil count lower than $500/mm^3$, according to National Institute for Health and Clinical Excellence guidance.[14,15]

Invasive Fungal Infections

EORTC/MSG[13] has standardized the pathological characteristics of proven/probable/possible fungal infection based on host factors, clinical criteria, and mycological criteria.[9] They are as follows:

- Possible IFI—the absence of mycological evidence but the presence of both clinical and host factors.
- Probable IFI—the presence of all criteria: imaging studies showing features suggestive of fungal infection and mycological evidence of fungal elements from sputum, bronchoalveolar lavage, sinus aspirate using cytology/direct microscopy/culture, or detection of antigen/cell wall constituents (such as beta-galactomannan and beta-glucan).
- Proven IFI—histopathological/cytopathologic/microscopic evidence from normally sterile sites showing the fungal organism with evidence of tissue destruction or blood culture growth of a fungal organism.

Statistical Analysis

The data were coded in an excel sheet and fed into IBM Statistical Package for the Social Sciences version 25.0, Armonk, NY, United States for analysis. Frequency and percentage were used to express categorical variables, and continuous variables were expressed with mean and standard deviation. The groups were compared using one-way analysis of variance test to state their significance. The relationship between AFP and invasive fungal disease was tested using binary logistic regression. The associations of IFI with risk factors were analyzed using the chi-square test. p-Value < 0.05 was considered statistically significant in a two-tailed test.

Results

Study Population, Patient Characteristics, and Overall Invasive Fungal Infection

A total of 55 out of 80 NCI high-risk ALL children fulfilled the inclusion criteria (►**Fig. 2**). For the rest of the children, either information was inadequate or they were transferred to other centers for management soon after the diagnosis. Among 55 children, 41 children had a high WBC count of $\geq 50,000/mm^3$, 12 children had T cell ALL, and 2 children were aged above 10-year-old with a WBC count of $<50,000/mm^3$.

Children were almost equally distributed among regimens B and C following induction (26 and 29, respectively). In our cohort, the total incidence of IFI was 51% (28/55). Out of the 55 children, 33 (60%) of them were on AFP, and among them, only 12 (28%) had a fungal infection (►**Table 1**). Out of

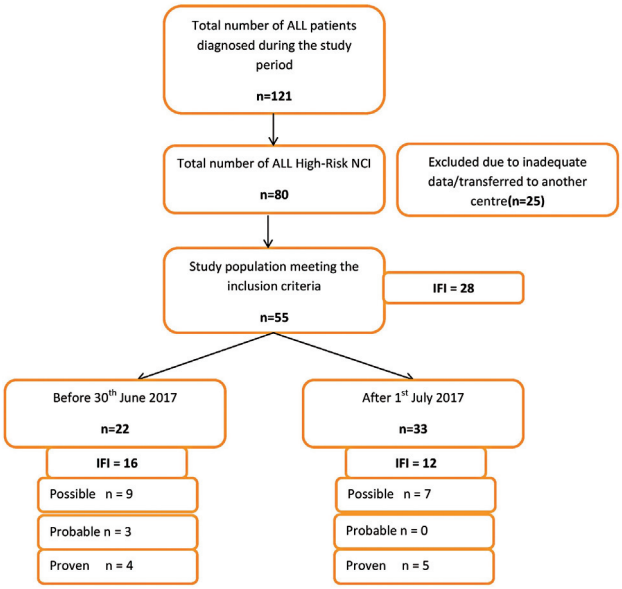

Fig. 2 Flow diagram depicting the study design.

22 children (40%) who were not on AFP, 16 of them developed a fungal infection (70%; p-Value = 0.008).

The characteristics of 28 children with IFIs are summarized in ►**Table 2**. Children between the age of 1 and 10 years ($p = 0.012$) on regimen C and boys were predominantly affected. IFI was noted more commonly in these phases of treatment: induction in 50% (14 out of 28) of patients followed by consolidation in 25% (7 out of 28) of patients and delayed intensification in 25% (7 out of 28) of patients. As per the EORTC/MSG guidelines, on the classification of IFIs, possible infection was seen in 57% (16 out of 28) of the children, followed by proven infection in 32% (9 out of 28) of the children and probable infection in 11% (3 out of 28) of the children.

All children, irrespective of their IFI classification, underwent a chest X-ray and ultrasonography (100%). Echocardiography was performed in 15 patients (27%) out of 55 with IFI, and all were found to be normal. In addition, imaging studies such as CT scan for chest and sinuses; MRI brain based on medical history and examination was performed. A total of eight patients were screened by these techniques, and it was found that two patients had fungal pneumonia, two patients had fungal frontal sinusitis and mastoiditis, and three patients had fungal granulomas in the brain.

All the children diagnosed with probable IFI had an estimation of serum galactomannan, which was >0.5 IU/mL (normal <0.5 IU/mL), indicating *Aspergillus* infection. In children with proven infection, *Candida species* ($n = 11$) were the most common organisms isolated. Among them, *C. parapsilosis and C. tropicalis* (44%) were the predominant fungal species isolated.

Possible Invasive Fungal Infection

Among 57% of the children (16/28) with a possible infection, most had a fungal disease in their induction phase of chemotherapy, and 50% (8 out of 16) developed a fungal infection on prophylaxis. Ultrasonography performed on the abdomen picked up the liver and splenic granuloma, suggesting candidiasis in two children. One had a sinus infection out of the two screened, and two out of three had fungal pneumonia (67%).

Probable Invasive Fungal Infection

Probable infections were more common in 67% (two out of three) of the patients during the delayed intensification phase of treatment, and 67% of them developed a fungal infection on prophylaxis. The three children with fungal brain granuloma presented with seizures/altered sensorium/focal neurological deficit.

Proven Invasive Fungal Infection

Thirty-three per cent of children with proven infection predominantly developed the fungal disease during the induction phase of chemotherapy. However, there was not much difference in the other phases where (5 out of 9) 56% of the children were on prophylaxis. *C. parapsilosis and C. tropicalis* were the predominant fungi isolated.

Table 1 Characteristics of the study population

Total number of patients diagnosed with high-risk ALL during the study period		55
Age	1–10 y	38 (69%)
	≥10 y	17 (31%)
Sex	Male	36 (65%)
	Female	19 (35%)
UKALL 03 regimen	B	26 (53%)
	C	29 (47%)
No. of children on AFP		33 (60%)
No. of children with fungal infection on AFP		12 (33%)
No. of children without AFP		22 (40%)
No. of children with fungal infection not on AFP		16 (73%)

Abbreviations: ALL, acute lymphoblastic leukemia; AFP, antifungal prophylaxis; UKALL, United Kingdom Acute Lymphoblastic Leukemia.

Table 2 Characteristics of children with invasive fungal infection

Total number of children with fungal infection		28 (51%)		*p*-Value
Age	1–10 y	19 (68%)		*0.012*
	>10 y	9 (32%)		
Sex	Male	15 (54%)		0.706
	Female	13 (46%)		
UKALL 03 regimen	B	10 (36%)		0.136
	C	18 (64%)		
Central line	Present	7 (25%)		*0.012*
	Absent	21 (75%)		
Type	Chemoport	5 (71%)		
	Femoral	2 (29%)		
Phase	Induction	14 (50%)		
	Consolidation	7 (25%)		
	Delayed intensification	7 (25%)		
IFI	Possible	16 (57%)		
	Probable	3 (11%)		
	Proven	9 (32%)		
Investigations	Chest X-ray	28		
	Blood culture	28		
	Candida Albicans	2 (22%)		
	Candida parapsilosis	4 (44%)		
	Candida krusei	1 (12%)		
	Candida Tropicalis	4 (44%)		
	Galactomannan level (Aspergillus)	3/3		
	Imaging	USG abdomen	2	
		CT sinuses	2	
		CT/MRI head	3	
		CT chest	2	
		2D Echo	15 (54%)	

Abbreviations: 2D, two dimensional; CT, computed tomography; IFI, invasive fungal infection; MRI, magnetic resonance imaging; UKALL, United Kingdom Acute Lymphoblastic Leukemia; USG, ultrasonography.

Invasive Fungal Infection and its Risk Factors

According to our study, the presence of an associated bacterial infection increases the risk of IFI, but the sample size was minimal to calculate the odd's ratio ($p = 0.04$). Children had a concurrent bacterial infection, and the causative organisms were *Klebsiella pneumonia* in two children with associated *Enterococcus* in one, *Pseudomonas aeruginosa* in another, and the last child with *Escherichia coli*. There was no significant association between IFI with age ($p = 0.083$), gender ($p = 0.054$), in-situ central line ($p = 0.70$), and regimen ($p = 0.68$; ►**Table 3**).

Table 3 Risk analysis of invasive fungal infection with its risk factors

Variable	Odd's ratio with 95% confidence interval	*p*-Value
Gender	0.33 (0.1–1.1)	0.054
Central line	0.79 (0.24–2.6)	0.70
Associated bacterial infection	–	0.04
Age	1.8 (0.6–5.6)	0.083
Final regimen	1.25 (0.43–3.61)	0.68

Antifungal Prophylaxis and Invasive Fungal Infection

The most common antifungal prophylactic agent administered was voriconazole in 26 children (79%) at 6 mg/kg/dose twice daily, followed by itraconazole in 4 children (12%). One child was on fluconazole prophylaxis, and another one was on an alternate day dosage of amphotericin B.

Out of the two groups, 33 children (60%) were on AFP, 22 (40%) were not on prophylaxis, and no significant differences in age, gender, treatment regimen, presence of central line, and or associated bacterial infection between the two groups were found. However, we found a statistically significant difference in IFI (11 out of 33 vs. 16 out of 22; $p = 0.008$), signifying incidence of fungal infection was lesser in children on AFP (►**Supplementary Table S1**). Our study established the relationship between AFP and IFI using binary logistic regression analysis. According to our study, children off AFP were discovered to be 4.7 times (95% confidence interval: 1.44–15.13, Nagelkerke R^2 0.166, Wald 6.589, $p = 0.007$) more likely to get IFI than children on AFP.

Discussion

Our present study showed that the overall incidence of fungal infection was 51% in high-risk ALL cases. Other Indian studies have shown a wide range of IFI prevalence from 6.6 to 74.6% in ALL children, but they have not shown the incidence in high-risk children. Studies worldwide have shown a high incidence rate of IFI in ALL children, more specifically in the high-risk group.[16,17] An 8-year study in Indian children has shown a 6.6% incidence of IFI and a 44% mortality rate in ALL children.[18] In our study, the induction phase of chemotherapy accounted for the maximum number of cases of invasive fungal disease like other previously published[19,20]

There are multiple risk factors associated with the emergence of a fungal infection in a child.[21] From our study, associated bacterial infection was identified as a risk factor. Age, central venous access, or gender did not increase the chance of fungal infection. The other likely reasons for increased prevalence in our center are the use of dexamethasone during induction and an environment where the increased humidity helps spores of molds to grow and stay for a longer duration.[22] The incidence and the outcome of IFI in ALL children in low- and middle-income countries are shown in ►**Table 4**. According to a study conducted in Australia, the prevalence of fungal infection in developed countries was only around 9.7%.[23]

IFIs were more common in children from 1 to 10 years in regimen C, but a statistically significant correlation between age with IFI was not found in our study ($p = 0.083$). Previous studies have shown that an increase in age increases the risk of IFI.[21,24,25]

All the children with possible infection were either diagnosed clinically or based on imaging findings suggestive of fungal infection. All children with probable infections had documented serum galactomannan levels. Serum galactomannan is a very useful biomarker as most cultures turn up sterile, and invasive tissue diagnosis is not always feasible in this population. It has a sensitivity of about 60 to 80% and excellent specificity of 80 to 95%.[26] Among the species isolated in our cultures, *Candida* species that are not *Candida albicans* (45%) especially *C. parapsilosis* are found to be predominant compared to *C. albicans,* as reported in other studies as well.[20,22,24,25]

The antifungal agent commonly used for primary prophylaxis in our study was voriconazole (75%). All the children tolerated the drug well, and no adverse reactions were noted. Dorthea et al, in their prospective multicentric study predominantly involving children with ALL, found voriconazole prophylaxis to reduce the incidence of IFI, and only one breakthrough fungemia and manageable adverse effects were noted. It had established the safety and tolerability of voriconazole in children[27] but not in all studies.[28] In their pediatric AFP guideline for 2014, Science et al found the moderate quality of evidence in starting AFP in ALL patients.[8] The other few antifungal agents such as amphotericin B, fluconazole, and echinocandins have been studied; however, not enough evidence is available to suggest routine use of these drugs. A study on the use of fluconazole prophylaxis in acute leukemia in children also indicated a reduction in IFI incidence. Still, it did not establish the safety data of fluconazole.[8] The randomized controlled trial performed to compare the efficacy of voriconazole and low dose amphotericin B in pediatric ALL showed better results with voriconazole in efficacy and safety profile.[29] International guidelines state that voriconazole is the recommended antifungal for high-risk ALL children. It is administered at oral doses of 9 mg/kg/d twice daily (BD) (maximum dose 350 mg) for age 2 to 14 years or <50 kg, 200 mg BD for age >15 years or > 50 kg; IV doses of 8 mg/kg/d BD (day 1: 9 mg/kg) for age 2 to 14 years or < 50 kg and 4 mg/kg BD (day 1: 6 mg/kg) for age >15 years or >50 kg with regular therapeutic drug monitoring (trough 1–3 µg/mL). Liposomal amphotericin-B thrice weekly or echinocandin are other alternatives. In our center, it is a practice to withhold antifungal azoles one day before vincristine injection as it worsens the vincristine toxicity,[30] and restart it 24 to 48 hours later. This might also be a reason for an increased incidence of breakthroughs. Previous studies have reported 27% IFI in pediatric oncology patients (9% in ALL) while on caspofungin prophylaxis,[31] 3.1% of HSCT transplant children developed IFI on micafungin prophylaxis,[32] and 6.7% of AML children had breakthrough IFI on voriconazole prophylaxis,[33] but not in all.[28]

The incidence of fungal infection in children on AFP was only 28% compared to 70% in the control group in our study. AFP drastically reduced the rate of IFI in high-risk ALL children, and we found a 65% reduction in incidence according to our study. Though enough evidence is not available to recommend routine use of AFP in ALL children, the incidence of IFI is high in children belonging to a high-risk group. As shown by our study and previous studies also, the burden of fungal infection is high in Asian countries. However, the exact incidence in India is not available.[34,35] The latest 2020 clinical practice guidelines by Lehrnbecher

Table 4 Incidence and outcome of IFI in children with ALL in low- and middle-income countries

Author (Ref)	ALL-HR (Y/N)	IFI incidence in ALL	Time period	Cases (*N*)	Mortality	AFP (A/P)	Type of study	Analysis
Kumar et al[37]	N	14/17 (74.6%)	2013–2014	59	4/7(57%) in the induction phase	A	Prospective study—New Delhi	Prevalence of IFI is very high in children with persistent febrile neutropenia who are not on AFP.
Tüfekçi et al[38]	Y	7/17 (41%)	2001–2013	174	NR	A	Retrospective study—Turkey	Higher prevalence of IFI with persistent febrile neutropenia in HR-ALL children.
Evim et al[39]	Y	84/238 (35.2%) with 18 (21%) in HR blocks	2010–2015	238/289	34%	P-26/87 developed on IFI—fluconazole followed by Itraconazole	Retrospective study—Turkey	Increased IFI in high-risk ALL children even on AFP and higher mortality rate.
Kaya et al[19]	N	10/106 (10.2%)	1998–2007	106/154	5%	P	Retrospective study—Turkey	AFP with fluconazole may be reducing the incidence and mortality of IFI.
Supatharawanich et al[40]	N	12/150 (8%)	2009–2019	150/241	8.3%	P-4/12 had IFI on AFP (itraconazole and posaconazole)	Retrospective study—Thailand	AFP reduces IFI in relapsed leukemia but not in ALL children.
Yi et al[41]	N	65/214 (30.7%)	2014–2017	214	NR	A	Retrospective study—PR China	The occurrence of IFI in children with ALL relates to the time of hospitalization and the level of neutrophils.
Zhang et al[42]	Y	63/155 (40.6%)	2017–2018	155	NR	P-45% IFI—No AFP vs. 37% on AFP (posaconazole and fluconazole)	Retrospective study—PR China	Incidence of IFI with AFP was comparable between the two groups (on AFP vs. off AFP).
Das et al[18]	N	46/55 (83%)	2006–2013	692	44%	A	Retrospective study—India	IFI most common cause of treated related mortality in pediatric ALL.
Bal et al[43]	N	24/125	2005–2013	125	13.3%	A	Retrospective study—Turkey	Younger age, prolonged neutropenia, and induction phase chemotherapy were considered risk factors for IFI.

Abbreviations: ALL, acute lymphoblastic leukemia; AFP, antifungal prophylaxis; HR, high risk; UKALL, United Kingdom Acute Lymphoblastic Leukemia; IFI, invasive fungal infection.

et al state that consider administering systemic AFP to children and adolescents with newly diagnosed and relapsed ALL at high risk for IFI. However, they state low quality of evidence and weak recommendation due to the absence of comprehensive IFI incidence data in low-risk ALL children therefore warranting further protocol-specific recommendation and are strictly against the use of routine IFP in low-risk ALL children.[36]

Limitations

It was a retrospective study and, therefore, subject to certain limitations inherent in its design. For example, the use of preexisting case records makes it difficult to obtain information on potential confounding variables. In addition, it had a relatively small sample size.

Conclusion

This study showed that the incidence of IFI can be remarkably high among children with high-risk ALL during intensive phases of therapy, and the use of AFP reduces the incidence of IFI in these children. From these findings, therefore, the routine use of AFP during the intensive phase of chemotherapy in high-risk pediatric ALL children may be considered.

Declarations

Ethics statement

Ethical Approval (Including Committee and Record Number)

Permission granted by the Institutional Ethics committee of Kasturba Medical college hospital Mangaluru on (IEC KMC MLR 02-2021/71)

Informed Consent

Consent has been obtained initially at the time of commencement of treatment to collect the data on characteristics of acute lymphoblastic leukemia, treatment regimens, and febrile neutropenia episodes.

Author Contribution

N.S. collected and analyzed the data and drafted the manuscript, and H.P.L. conceived the idea and reviewed and edited the manuscript.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

We would like to thank the families and children for their participation, and Miss Madhura Kishore and Miss Shobha Naik for collecting the data.

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