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Frequency and Treatment Outcome of Invasive Fungal Infections in Children with Hematological Malignancies

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ABSTRACT

Background: Invasive fungal infections are the cause of significant morbidity and mortality among cancer patients of any age group. This research aimed to determine the frequency and treatment outcome of invasive fungal infections in children with hematological malignancies.

Methods: This cohort study was performed at the Department of Pediatric Oncology, Combined Military Hospital, Rawalpindi, Pakistan, from January 2022 to June 2023. Children of either gender aged less than 18 years diagnosed with hematological malignancies were included adopting a non-probability consecutive sampling technique. Treatment followed "Berlin-Frankfurt-Münster (BFM)" based protocols. Outcome in the form of mortality was noted by the end of the study period.

Results: A total of 240 cases of various types of hematological malignancies during the study period and 41 (17.1%) cases were found to have invasive fungal infections. In 41 invasive fungal infections, 28 (68.3%) were male. The mean age was 6.35±3.72 years. Invasive fungal infection was found to be possible, probable, and proven in 34 (82.9%), 6 (14.6%), and 1 (2.4%) cases respectively. Amphotericin B was the most frequent anti-fungal, advised in 23 (56.1%) cases whereas voriconazole was given in 14 (41.5%) patients. The mean duration of treatment was 21±19 days (ranging between 2 to 84 days). Mortality was reported among 10 (24.4%) cases.

Conclusion: The frequency of IFS was 17.1% among children with hematological malignancies. Mortality was relatively high (24.4%) among children with IFIs which warrants early identification and treatment of IFIs among children with hematological malignancies.

Keywords: Amphotericin B, Acute Lymphoblastic leukaemia, Acute Myeloid leukaemia, Invasive Fungal Infection, Voriconazole.

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INTRODUCTION

Invasive fungal infections (IFIs) are the cause of significant morbidity and mortality among cancer patients of any age group[1]. IFIs are more likely to develop (approximately 10% or more) in patients having "acute myeloid leukemia (AML)", recurrent acute leukemia, high-risk acute lymphoblastic leukemia, and recipients of allogeneic "hematopoietic stem cell transplantation (HSCT)" in particular[2]. The increased use of chemotherapeutic agents in heavy doses has heightened immunosuppression, raising the occurrence of IFIs[3]. Although non-culture methods for detecting infections like β-glucan and galactomannan assays, lateral-flow devices, and fungal "polymerase chain reaction (PCR)" have emerged, their standardization is incomplete, and limitations persist.[4] Despite progress in nonculture-based methods and antifungal treatments, promptly diagnosing and managing IFIs remains challenging. "European Organization for Research and Treatment of Cancer / Invasive Fungal Infections Cooperative Group and The National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG)" describes IFIs as proven, probable, or possible[5]. Data shows that in 7.4% patients experiencing allogeneic HSCT had proven and probable invasive lillness[6]. Proven and probable Invasive mold illnesses have been found to be 17.9% more common in AML patients receiving their first remission-inducing treatment[7]. These studies mainly targeted the adult population[5,6,7,8].

Unfortunately, insights from adult studies are not directly applicable to children, given their distinct underlying malignancies, treatments, outcomes, and fewer age-related comorbidities. Moreover, advancements in diagnostic tests, antifungal agents, and supportive care algorithms have improved outcomes of IFIs in the recent decades.[5,6] Understanding the local epidemiology and outcomes of IFIs is crucial for designing antifungal treatment approaches for vulnerable populations. Unfortunately, there is limited local data characterizing IFIs in pediatric hematological malignancy cases in Pakistan. The objective of this study was to determine the frequency and treatment outcome of invasive fungal infections in children with hematological malignancies.

METHODS

This cohort study was performed in the Department of Pediatric Oncology, CMH, Rawalpindi, Pakistan, from January 2022 to June 2023. Approval from the "Institutional Ethical Committee" was obtained (letter number: 456). Informed and written consents were acquired from parents/guardians of all patients. Children of either gender aged less than 18 years diagnosed with hematological malignancies were included. Parents or guardians of children who refused to be part of this study were excluded from this study. No specific sample size calculations were made for this research and we included all cases fulfilling the inclusion criteria and avoiding the exclusion criteria. Non-probability consecutive sampling technique was adopted.

Fever entailed a temperature exceeding 38.5°C once or 38-38.5°C twice within 4 hours. Neutropenia had an absolute neutrophil count ≤500/mm. β-d-Glucan above 80 pg/ml was nominated as raised. Invasive fungal disease (IFD) was defined as a proven, probable, or possible infection as per the EORTC/MSG consensus group.[5] Proven IFD "require detection of a fungus by culture in blood or an otherwise sterile compartment, or histopathological evidence of fungal elements in affected tissue"[5]. Probable IFD was defined by "the presence of host factors (e.g., severe and prolonged neutropenia, allogeneic HSCT), clinical criteria [e.g., lower respiratory tract infection with computerized tomography (CT) imaging demonstrating lesions suggestive of an IFD], and mycological criteria [e.g., culture of a mold in sputum or broncho-alveolar lavage (BAL), detection of galactomannan (GM) in serum (optical density index of >1.0 (one sample) or >0.5 (two samples) or BAL (cut-off 1.0)]". PCR-positive test results were not considered as a determining factor for classifying a fungal infection as a probable IFD. Instead, patients who exhibited suitable host factors and presented significant clinical evidence indicative of IFD, but lacked mycological confirmation, were categorized as individuals with possible IFD.

Demographic and disease-related data, laboratory diagnostics, imaging, and antifungal drug use information were recorded. Treatment followed "Berlin-Frankfurt-Münster (BFM)" based protocols. Empirically supported or preventative mold-active antifungal agents were administered accordingly. Antifungal prophylaxis varied as per local standard procedures. Data analysis was performed using "Statistical Package for Social Sciences (SPSS)", version 26.0. The chi-square test was used to compare data considering $p<0.05$ as significance.

RESULTS

A total of 240 cases of various types of hematological malignancies during the study period and 41 (17.1%) cases were found to have invasive fungal infections. These 41 (17.1%) cases of invasive fungal infections were further analyzed. In 41 invasive fungal infections cases, 28 (68.3%) were males. The mean age was 6.35±3.72 year ranging between 1 to 14 years. Most common type of disease was acute lymphoblastic leukaemia, 20 (48.8%), while 12 (29.3%) cases were of acute myeloid leukaemia. The most frequent types of signs and symptoms were fever, cough, chest crepitation,

and shortness of breath, reported in 38 (92.7%), 26 (63.4%), 14 (34.1%), and 13 (31.7%) cases respectively (table-1). High-resolution computed tomography (HRCT) findings revealed alveolar opacities/nodules, and ground glass haze/opacities as the most frequent findings, observed in 13 (31.7%) cases each, respectively

Table 1: Demographic and Clinical Characteristics (n=41)

Characteristics		Frequency (%)
Gender	Male	28 (68.3%)
	Female	13 (31.7%)
Age (years)	<5	17 (41.5%)
	5-12	20 (48.8%)
	13-14	4 (9.8%)
Disease type	Acute lymphoblastic leukaemia	20 (48.8%)
	Acute lymphoblastic leukaemia relapse	7 (17.1%)
	Acute myeloid leukaemia	12 (29.3%)
	Acute myeloid leukaemia relapse	2 (4.9%)
Frequency of signs and symptoms	Fever	38 (92.7%)
	Shortness of breath	13 (31.7%)
	Cough	26 (63.4%)
	Chest crepitation	14 (34.1%)
	Cyanosis	3 (7.3%)
	Mucositis	2 (4.9%)
	Abdominal pain	1 (2.4%)
High-resolution computed tomography findings	Alveolar opacities / Nodules	13 (31.7%)
	Ground glass haze/opacities	13 (31.7%)
	Aspergillosis	5 (12.2%)
	Pleural effusion	4 (9.8%)
	Cavitatory lesions / Nodules	3 (7.3%)
	Tree in bud appearance	1 (2.4%)
	Nodules in liver and spleen	1 (2.4%)
	Atelectasis	1 (2.4%)

Table 1: shows details about the demographics, and clinical and radiological findings of patients.

Figure 1 shows HRCT findings of a patient showing multiple round opacities in bilateral lung parenchyma with ground glass opacities.

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Figure-1: Multiple Round Opacities in Bilateral Lung Parenchyma with Ground Glass Opacities

All patients had neutropenia. β-d-Glucan was raised in 6 (14.6%) cases. Blood culture was negative in all 41 cases as no growth was found in samples of any of the cases. Invasive fungal infections were found to be possible, probable, and proven in 34 (82.9%), 6 (14.6%), and 1 (2.4%) cases respectively. Amphotericin B was the most frequent anti-fungal, advised in 23 (56.1%) cases whereas voriconazole was given in 14 (41.5%) patients. One patient (2.4%) was advised of Posaconazole. The mean duration of treatment was 21±19 days (ranging between 2 to 84 days). Mortality was reported among 10 (24.4%) cases while the remaining 31 (75.6%) patients improved.

Table 2: Comparison of Disease Types Concerning Gender, Age, Invasive Fungal Infection Type, and Outcomes

Variables		Disease Types				P-value
		Acute lymphoblastic leukaemia (n=20)	Acute lymphoblastic leukaemia relapse (n=7)	Acute myeloid leukaemia (n=12)	Acute myeloid leukaemia relapse (n=2)	
Gender	Male	13 (65.0%)	6 (85.7%)	8 (66.7%)	1 (50.0%)	0.704
	Female	7 (35.0%)	1 (14.3%)	4 (33.3%)	1 (50.0%)	
Age (years)	<5	13 (65.0%)	1 (14.3%)	2 (16.7%)	1 (50.0%)	0.121
	5-12	6 (30.0%)	5 (71.4%)	8 (66.7%)	1 (50.0%)	
	13-14	1 (5.0%)	1 (14.3%)	2 (16.7%)	-	
Invasive fungal infection	Possible	16 (80.0%)	5 (71.4%)	12 (100%)	1 (50.0%)	0.394
	Probable	3 (15.0%)	2 (28.6%)	-	1 (50.0%)	
	Proven	1 (5.0%)	-	-	-	
Outcomes	Mortality	3 (15.0%)	4 (57.1%)	3 (25.0%)	-	0.128
	Improved	17 (85.0%)	3 (42.9%)	9 (75.0%)	2 (100%)	

Table 2 shows showing comparison of disease types concerning gender, age, invasive fungal infection type, and outcomes. No statistically significant associations were observed (p>0.05). Mortality rates were reported to be in ALL, ALL relapse, AML, and AML relapse patients as 15.0%, 57.1%, 25.0%, and 0% but these findings remained statistically insignificant.

DISCUSSION

In the present study, the prevalence of IFIs was noted to be 17.1% among children with hematological malignancies. Amphotericin B was the most frequent anti-fungal, used in 56.1% of cases whereas voriconazole was given 41.5% of patients. The mean duration of treatment was 21±19 days (ranging between 2 to 84 days). Of patients, 75.6% improved following anti-fungal treatment. Our study employed a stringent classification system for invasive fungal infections, providing insights into the spectrum of disease severity. The diverse antifungal treatment approaches, including Amphotericin B, voriconazole, and Posaconazole, reflected the complexity of managing these infections.

In a study conducted by a study from Taiwan, the overall occurrence rates of IFIs and confirmed/probable IFIs in pediatric patients with AML were 20.5% and 11.5% respectively[1]. Another study revealed that blood culture sensitivity for diagnosing invasive candidiasis and aspergillosis was only 21.3% and 1.1% respectively, when compared to autopsy-confirmed infections.[9] Mor et al found that the prevalence of all IFIs and confirmed/probable IFIs was 39.4% (26 out of 66) and 13.6% (9 out of 66) respectively[10]. In another study, Kobayashi et al documented an IFI frequency of 21.6% (11 out of 51)[11]. The study pointed to a frequency of around 5% for confirmed/probable IFIs[12,13].

In this study, 41 patients were included that had proven, probable, or possible IFDs. The percentage of possible IFDs in this study was higher than in previous studies, possibly resulting from comprehensive imaging studies performed when signs and symptoms suggested IFD presence despite negative microbiological tests[11,14]. Study designs, IFI definition, characteristics of studied cases, and treatment protocols were somewhat different in the studies that prevent direct comparisons.

Our study findings reported that children with ALL face a higher IFD risk compared to those with AML or with relapsed leukaemia, this group needs deep analysis for various reasons. Pediatric cancer patients with ALL represent the largest IFD risk group, and the greatest number of IFD diagnoses occur in pediatric ALL patients[15]. While most researchers do not differentiate among ALL risk groups that receive varying treatment intensities affecting IFD risk, our study reveals a considerably high IFD frequency in ALL patients[16]. Optimizing antifungal prophylaxis indication and duration is possible. However, accurately predicting individual IFD risk in ALL patients remains unclear. Our analysis exhibited 75.6% favorable response rate (complete or partial remission) among patients. The significantly reduced mortality relative to earlier studies was possible because of improved supportive care, advanced diagnostic tools, and access to potent antifungal compounds[17-19]. Data from Italy reported the mortality rate in IFIs to lie between 30-80% [20]. Reports exhibiting high mortality rates from the US (50%) are also on view but the duration of the evaluation period is an important factor when we describe mortality rates of IFIs among hematological malignancy cases[21]. In AML, mortality rates due to IFIs range between 20-50% whereas data from Greece showed that reported mortality rates in IFIs range between 20-70%[22]. Differences in mortality rates due to IFIs could be attributed to the extent of immune suppression, related factors, site as well as severity of infection, underlying pathology, and time to treatment initiation [23, 24, 25].

Being a single-center study and a relatively small overall sample size of IFI cases of this study were some of the limitations of this study. Further prospective trials should be planned to further estimate the existing and future burden of IFIs among children with hematological malignancies.

CONCLUSION

The frequency of IFSs among children with hematological malignancies was noted to be 17.1%. Acute lymphoblastic leukaemia emerged as the most common underlying disease, underlining the vulnerability of certain malignancies to fungal infections. A mortality rate of 24.4% underscores the critical nature of IFIs in pediatric hematological malignancies.

CONFLICT OF INTEREST

The authors have no conflict of interest.

ETHICAL APPROVAL

The permission was obtained from the Ethical Committee / Institutional Review Board of Combined Military Hospital, Rawalpindi, Pakistan through letter number 456, dated 26-09-2023.

AUTHORS CONTRIBUTIONS

RM did Data collection, drafting was responsible for the data's integrity; **RT** designed and conceived the idea, supervised, and proofread; **AAR** did manuscript editing, data analysis, and data interpretation; **QUA** did Manuscript editing, proofreading, and critical revisions; **AA** did Manuscript editing, data analysis, data interpretation; **FSR** did manuscript

editing, proofreading, critical revisions and approved for publication.

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