DOI: https://doi.org/10.54393/pjhs.v6i7.3143

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 07 (July 2025)

Original Article

OPEN ACCESS

Incidence of Fungal Pneumonia in Children with Acute Myeloid Leukemia Taking Oral Antifungal Prophylaxis

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ARTICLE INFO

Keywords:
Acute Myeloid Leukemia, Fungal Pneumonia, Invasive Fungal Disease, Antifungal Prophylaxis, Voriconazole, Posaconazole

How to Cite:
Iqbal, L., Riaz, S., Gull, S., Iqbal, I., Gull, A., & Ahmed, T. (2025). Incidence of Fungal Pneumonia in Children with Acute Myeloid Leukemia Taking Oral Antifungal Prophylaxis: Fungal Pneumonia with Acute Myeloid Leukemia Taking Oral Antifungal Prophylaxis. Pakistan Journal of Health Sciences, 6(7), 108-113. https://doi.org/10.54393/pjhs.v6i7.3143

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Received Date: 9th May, 2025
Revision Date: 22nd July, 2025
Acceptance Date: 26th July, 2025
Published Date: 31st July, 2025

ABSTRACT

Acute leukemia is common in children, with acute lymphoblastic leukemia (ALL) making up 80-85% and acute myeloid leukemia (AML) 10-15%. **Objective:** To determine the incidence of fungal pneumonia in children with acute myeloid leukemia taking oral antifungal prophylaxis. **Methods:** In this single-center retrospective study done in a tertiary care hospital, the study analyzed 276 pediatric AML cases from July 2022 to June 2024.The diagnosis of fungal pneumonia was made on the basis of CT scan findings.Demographic and AML subtype data were also analyzed. **Results:** Among the 276 AML patients enrolled in this study, the mean age of the patients was 8.4 years (range 1-16 years), and there was a male predominance (157 male vs. 119 female). The most common AML subtype was M2 (34.1%), followed by M4 (16.7%) and M5 (8.3%). Out of 276 patients with AML, 69 (25.0%) had CT findings suggestive of fungal pneumonia. M2 and M4 subtypes were the most commonly affected, accounting for about 50% of cases. **Conclusions:** Children with AML taking oral primary antifungal prophylaxis have a 25% incidence of fungal pneumonia. These findings highlight the importance of vigilant imaging surveillance and targeted interventions in high-risk subgroups (M2 and M4).

INTRODUCTION

Acute leukemia is common in children, with acute lymphoblastic leukemia (ALL) making up 80-85% and acute myeloid leukemia (AML) 10-15%. Childhood AML is the second most common hematological malignancy, arising from abnormal changes in stem cell precursors that typically mature into myeloid cells like white blood cells, red blood cells, and platelets [1, 2]. Etiological factors for childhood AML involve genetic syndromes (e.g., Down syndrome), hematological disorders (e.g., Fanconi anemia), and environmental factors (e.g., benzene exposure). High-risk factors include monosomy-7, alkylating agents, positive family history in identical twins, and Down syndrome (risk increased by 200-400-fold) [3]. Children with AML typically show various symptoms such as fever, bone pains, lethargy, pallor, skin nodules, ocular proptosis, and bleeding tendencies like nose bleeds and gum bleeding. Treatment options encompass chemotherapy, immunotherapeutics (e.g., gemtuzumab ozogamicin), targeted therapy (e.g., FLT3 inhibitors), and supportive care [4, 5]. Children with AML undergoing intensive chemotherapy face high infection risks: 50-60% for severe bacterial infections and 5-15% for invasive fungal infections. Supportive care guidelines advocate prophylactic use of systemic antibiotics and antifungals,

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granulocyte colony-stimulating factor (G-CSF), and mandatory hospitalization during severe neutropenia [6, 7]. Children with AML have increased infection risk from weakened immunity due to the disease and chemotherapy, which may be bacterial, viral, or fungal. Fungal infection is suspected with persistent fever during neutropenia despite broad-spectrum antibiotics [8]. In AML, myeloid cell dysfunction poses a higher risk of invasive fungal infections compared to lymphoid cell dysfunction in ALL. Additionally, profound neutropenia lasts longer after chemotherapy in AML (>10 days) than in ALL. Globally, fungal infection incidence in children with AML is 5% with oral antifungal prophylaxis and 20% without [9]. Yeasts (mainly candidemia and hepatosplenic candidiasis) and molds (mainly aspergillosis) are the main agents of invasive fungal infections affecting the lungs, sinuses, and brain [10]. Fungal pneumonia is a significant cause of morbidity and mortality, especially in acute myeloid leukemia, where around 90% of fungal infections occur. Patients typically show non-specific symptoms such as persistent fever, cough, vomiting, and respiratory difficulties. Chest HRCT is more sensitive and specific for diagnosis compared to chest radiograph, MRI, or PET scan [11, 12]. Radiographic findings indicate invasive fungal chest infection with pulmonary nodules and distinct signs like halo or ground glass appearance [13]. The current guidelines recommend mold-active antifungal prophylaxis for the incidence of IFD greater than 10% in conditions like AML, relapsed acute leukemia, allogeneic HCT, and high-risk ALL. Recommended options include voriconazole, posaconazole, or micafungin, available both orally and intravenously [14, 15]. Clinical approaches for treating invasive fungal infections include primary prophylaxis with antifungals throughout chemotherapy, empirical treatment for febrile neutropenia lasting 96 hours, and diagnostic-driven initiation of antifungals upon positive biomarkers or imaging. Pediatric patients with IFI often exhibit non-specific symptoms and imaging findings [16]. The rationale for this study is that invasive fungal infections usually remain undiagnosed and are a major cause of morbidity and mortality in children with hematological malignancy. In Pakistan, there is no data available on fungal pneumonia in children with acute myeloid leukemia.

This study aims to determine the incidence of fungal pneumonia in children with acute myeloid leukemia taking oral antifungal prophylaxis

METHODS

The single-center retrospective study was conducted at the Pediatric Oncology Department of the University of Child Health Sciences/The Children's Hospital Lahore, following Institutional Review Board approval (957/CH.UCHS). A single-center approach was adopted, building upon retrospective analysis of 276 pediatric AML cases from July 2022 to June 2024 using a non-probability consecutive sampling technique. A sample size of 276 was estimated by using a 95% confidence level, 4.34% margin of error and an expected percentage of fungal infections as 16.1% in children with AML [17]. The study enrolled children under 16 years of age diagnosed with acute myeloid leukemia who presented to the Outpatient Department and emergency room during the study period. Only those receiving oral antifungal prophylaxis while undergoing chemotherapy were included. Both genders were represented in the study population, while children over 16 years of age and those without evidence of invasive fungal infection were excluded. Eligible patients received oral antifungal prophylaxis consisting of either Tablet Voriconazole at 4 to 6 mg/kg/day or Tablet Posaconazole at a dose of 100 mg orally twice daily on the first day, followed by 100 mg once daily for 13 days. Fungal pneumonia was classified into three categories. Suspected fungal pneumonia included patients with one host factor, prolonged neutropenia with fever lasting more than 96 hours unresponsive to broad-spectrum systemic antibiotics, and respiratory symptoms, potentially requiring empirical antifungal therapy. Probable fungal pneumonia was defined by the presence of one host factor, a clinical or radiological parameter, and non-culture-based mycological evidence such as fungal antigen or β-D-glucan, necessitating pre-emptive antifungal therapy. Proven fungal pneumonia was diagnosed when a patient had one host factor, relevant clinical or radiological features, and either a positive fungal culture or histopathological evidence, justifying specific antifungal therapy. Host factors included hematological malignancy, receipt of stem cell or organ transplant, inherited immunodeficiency, prolonged use of immunosuppressive therapy, or acute graft-versus-host disease. Radiological indicators of fungal pneumonia, as observed on high-resolution chest CT (128 slice CT scan), comprised pulmonary nodules, halo sign, air crescent sign, ground-glass opacification, or cavitation, suggesting pneumonitis, pneumonic consolidation, or fungal cavitations. Each patient's age, sex, presenting complaints, and HRCT (HRCT chest interpretations were standardized using predefined radiological criteria for fungal pneumonia features. Two experienced pediatric radiologists independently reviewed all scans, with disagreements resolved through consensus discussion. A standardized reporting template was used to document specific findings (ground glass appearance, pulmonary nodules, halo sign, cavitation, consolidation). Chest findings were recorded. A structured proforma was used to document all relevant clinical and radiological details. Patients were followed throughout the study duration to monitor the development and classification of fungal pneumonia. The diagnosis of AML was confirmed on

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flow cytometry, identifying AML-specific markers including CD11b, CD13, CD14, CD15, CD33, CD36, and CD41 (also referred to as platelet antiglycoprotein IIb/IIIa), CD42 (glycoprotein Ib), CD61 (glycoprotein IIIa), CD64, CD117 (cKIT), CD163, lysozyme, and MPO. FAB M1 and M2 subtypes have high levels of CD13, CD15, CD33, CD117, MPO, and often the stem cell marker CD34. FAB M3 has decreased to absent expression of HLA-DR (class II), CD11b and CD11c antigens. FAB M4 subtype has CD14, CD36, CD64, CD68, CD163, and lysozyme, all monocyte lineage-associated antigens, along with more typical myeloid markers, CD13, CD15, and CD33. FAB M4 AML also tends to express CD11b and CD11c antigens. FAB M5 subtype typically shows a decrease or loss of expression of CD13 but retains expression of CD14, CD15, and CD33, as well as CD36, CD11b, CD11c, CD64, and CD68, often on a single population of leukemic blasts. FAB M6 characteristically express the erythroid marker glycophorin A on the erythroblasts. FAB M7 typically expresses platelet glycoproteins, such as CD41, CD42, and CD61, along with CD13, CD33, and often CD36. Adherence was monitored through: (1) Weekly medication reconciliation during hospital visits, (2) Patient/caregiver medication diaries, (3) Pill counts at each visit, (4) Therapeutic drug monitoring when clinically indicated, (5) Documentation of missed doses and reasons. Patients with <80% adherence were excluded from analysis to ensure the prophylaxis effectiveness evaluation. Data completeness was ensured through: (1) Prospective data collection using standardized case report forms, (2) Weekly database monitoring for missing values, (3) Regular follow-up calls for missed appointments, (4) Electronic medical record integration for automatic data capture, and (5) Data verification by two independent research coordinators. For statistical analysis, SPSS version 24 was used. Quantitative variables were expressed as means with standard deviations, while qualitative variables were presented as frequencies and percentages. The Chi-square test was applied to evaluate associations between age, gender, and the occurrence of fungal pneumonia to determine statistical significance.

RESULTS

The study examined 276 AML patients with a mean age of 8.4 ± 2.65 years (range 1-16 years) with male predominance (56.9%). Patients were almost equally distributed between age groups 1-8 years (51.1%) and 9-16 years (48.9%). The most frequent AML subtype was M2 (34.1%), followed by M4 (16.7%), M5 (8.3%), and others (40.9%). Laboratory assessments revealed a mean hemoglobin of 8.41 ± 2.65 g/dL, mean total leukocyte count of 29.90 ± 1.34×10^9/L, mean platelet count of 41.94 ± 1.54×10^9/L, and mean blast percentage of 38.8%. Fungal pneumonia was identified in 69 patients (25.0%), predominantly affecting M2 and M4 subtypes (approximately 50% of cases). The most common CT findings were Ground Glass Appearance (20.7%) and Pulmonary Nodule (20.3%), followed by Consolidation (9.4%), Cavitation (5.1%), and Halo Sign (4.7%).

Table 1: Demographic, Clinical Characteristics, Laboratory Parameters, Fungal Pneumonia Characteristics and CT Findings of AML Patients

Variables	Mean ± SD/ n (%)
Clinical Characteristics	
Mean Age (Range)	1-16 Years: 8.4 ± 2.65
Gender Distribution	Males: 157 (56.9%)
	Females: 119 (43.1%)
Age Groups	1-8 Years: 141 (51.1%)
	9-16 Years: 135 (48.9%)
AML Subtypes	M2: 94 (34.1%)
	M4: 46 (16.7%)
	M5: 23 (8.3%)
	Others: 113 (40.9%)
Laboratory Parameters of AML Patients	
Hemoglobin	8.41 ± 2.65 g/dL
Total Leukocyte Count	29.90 ± 1.34×10^9/L
Platelet Count	41.94 ± 1.54×10^9/L
Blast Percentage	38.8%
Fungal Pneumonia Characteristics in AML Patients	
Total Patients with Fungal Pneumonia	69 (25.0%)
Most Common AML Subtypes	M2 and M4 (Approximately 50% of Cases)
CT Findings in AML Patients with Fungal Pneumonia	
Ground Glass Appearance	57 (20.7%)
Pulmonary Nodule	56 (20.3%)
Halo Sign	13 (4.7%)
Cavitation	14 (5.1%)
Consolidation	26 (9.4%)

When stratified by gender, fungal pneumonia affected 21.0% of male versus 30.3% of female (p=0.079), suggesting a non-significant trend toward higher female prevalence. Age-based stratification showed similar rates between younger (26.2%) and older children (23.7%) with p=0.627. The distribution of fungal pneumonia varied significantly across AML subtypes (p=0.009), with the highest rates in M5 (39.1%) and M2 (31.9%) subtypes, followed by other subtypes (23.0%), while M4 had the lowest incidence (8.7%) (Table 2).

Table 2: Stratification of Fungal Pneumonia in Patients with AML Concerning Different Variables

Variables		Fungal Pneumonia		p-Value
		Yes	No	
Gender	Male	33 (21.0%)	124 (79.0%)	0.079
	Female	36 (30.3%)	83 (69.7%)	
Age Groups	1-8 Years	37 (26.2%)	104 (73.8%)	0.627
	9-16 Years	32 (23.7%)	103 (76.3%)	

DOI: https://doi.org/10.54393/pjhs.v6i7.3143

AML Subtype	M2	30 (31.9%)	64 (68.1%)	0.009
	M4	4 (8.7%)	42 (91.3%)	
	M5	9 (39.1%)	14 (60.9%)	
	Others	26 (23.0%)	87 (77.0%)	

DISCUSSION

This retrospective study found that 25.0% of pediatric AML patients developed fungal pneumonia despite receiving oral antifungal prophylaxis.The mean age of our cohort was 8.4 ± 2.65 years with male predominance (56.9%), consistent with typical demographic patterns in pediatric AML.Our findings reveal important insights regarding fungal pneumonia in this high-risk population.The 25.0% incidence of fungal pneumonia observed in our study aligns with rates reported by Kobayashi *et al.* who documented invasive fungal infections in 21-30% of pediatric patients with hematologic malignancies [18]. Similarly, Fisher *et al.* reported cumulative incidence of invasive fungal disease ranging from 7.2% to 27.4% in children with AML despite prophylaxis, suggesting variable effectiveness of preventive strategies across different clinical settings [19]. Present study demonstrated significant variation in fungal pneumonia rates across AML subtypes (p=0.009), with M5 (39.1%) and M2 (31.9%) showing the highest prevalence compared to other subtypes (23.0%), while M4 had substantially lower rates (8.7%).This heterogeneity supports observations by Sung *et al.*who found that infection susceptibility differs across AML subtypes, potentially due to subtype-specific impacts on neutrophil function and immunological defenses [20].The particularly high risk in M5 subtypes may reflect the profound monocytopenia and dysfunctional granulocyte responses characteristic of this subtype, as previously documented by Lehrnbecher *et al.* [21].Radiologically, ground glass appearance (20.7%) and pulmonary nodules (20.3%) predominated in our cohort, followed by consolidation (9.4%), cavitation (5.1%), and halo sign (4.7%).These patterns are consistent with Greene *et al.*, comprehensive analysis of radiographic manifestations of invasive pulmonary aspergillosis, though current observed frequency of halo sign was lower than the 60-80% reported in some adult series.This discrepancy may reflect age-related differences in radiological presentation or variations in pathogen epidemiology [22].Regarding gender distribution, we noted a trend toward higher fungal pneumonia rates in female (30.3%) compared to male (21.0%), though this did not reach statistical significance (p=0.079).This finding contrasts with most published literature, which has not identified significant gender disparities in fungal infection susceptibility among pediatric AML patients. Castagnola *et al.* reported no gender-based differences in invasive fungal infection rates in their multicenter study of pediatric hematology patients [23]. Current age-stratified analysis showed comparable fungal pneumonia rates between younger (1-8 years: 26.2%) and older children (9-16 years: 23.7%) (p=0.627). This contrasts with Hovi *et al.* who reported higher infection risks in younger children due to immature immune systems and treatment-related factors.The absence of age-related differences in our cohort may reflect uniform application of prophylactic strategies across age groups [24].The 25% incidence of fungal pneumonia despite prophylaxis highlights important limitations in current preventive approaches.The breakthrough infections observed in our study align with findings from a multicenter trial by Maertens et al. which demonstrated that even with posaconazole prophylaxis, approximately 20% of high-risk patients still developed invasive fungal disease.This underscores the need for improved preventive strategies, particularly for high-risk AML subtypes [25].

CONCLUSIONS

It was concluded that children with AML taking oral primary antifungal prophylaxis have a 25% incidence of fungal pneumonia. These findings highlight the importance of vigilant imaging surveillance and targeted interventions in high-risk subgroups (M2 and M4).

Authors Contribution

Conceptualization: LI
Methodology: LI, SR, SG, II, AG, TA
Formal analysis: LI
Writing review and editing: LI, SG, II, AG, TA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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