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Prevalence of Pneumonia in Children with Acute Leukemia in the Oncology Wards of Teaching Hospitals in Urmia, Iran: A Retrospective Cross-Sectional Study

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Abstract

Background: Pneumonia is a major cause of morbidity and mortality in children with acute lymphoblastic leukemia (ALL). However, detailed regional epidemiological data are scarce. This study aimed to determine the prevalence and characterize the clinical profile of pneumonia among pediatric ALL patients in Urmia, Iran.

Methods: A retrospective cross-sectional study was conducted on children (≤18 years) with ALL admitted to oncology wards of teaching hospitals in Urmia from 2020 to 2023. Pneumonia was defined using modified Centers for Disease Control and Prevention (CDC) criteria. Data on demographics, clinical characteristics, microbiology, and outcomes were extracted from medical records. Period prevalence, incidence density, and risk factors were analyzed using appropriate statistical tests. Nutritional status was assessed using body mass index (BMI) z-scores, with underweight defined as a BMI z-score < -2 standard deviations.

Results: Of 150 eligible patients, 62 (41.3%) developed at least one episode of pneumonia, yielding a period prevalence of 41.3% (95% CI: 33.5–49.1%). Ninety-eight pneumonia episodes were identified, with an incidence density of 5.23 per 1000 patient-days. Most episodes (67.3%) were clinically diagnosed. Microbiological confirmation (32.7% of episodes) identified bacterial (62.5%), viral (25.0%), and fungal (12.5%) pathogens, with Pseudomonas aeruginosa being most common. Severe neutropenia (ANC <500 cells/μL) (adjusted OR: 4.2, 95% CI: 2.1–8.4; p<0.001) and high-risk ALL (adjusted OR: 2.8, 95% CI: 1.3–6.0; p=0.009) were independent risk factors. Underweight status was associated with increased pneumonia risk in univariate analysis (OR: 2.1, 95% CI: 1.1–4.0; p=0.03) but was not an independent predictor in multivariable analysis. Complications included intensive care unit (ICU) admission (22.4%) and pneumonia-associated mortality (6.1%).

Conclusions: Pneumonia is highly prevalent and severe in pediatric ALL patients in this setting, strongly associated with severe neutropenia and high-risk disease. Findings underscore the need for enhanced surveillance, optimized prophylaxis, and prompt management to mitigate this major infectious complication.

Key Words: Acute Lymphoblastic Leukemia, Child, Pneumonia, Prevalence.

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1- INTRODUCTION

Acute leukemia represents the most common childhood malignancy, accounting for approximately 30% of all pediatric cancers, with acute lymphoblastic leukemia (ALL) being the predominant subtype (1). Remarkable advances in multi-agent chemotherapy regimens over recent decades have significantly improved the overall survival rates for children diagnosed with acute leukemia, pushing five-year survival figures above 90% for standard-risk ALL in high-resource settings (2). However, this therapeutic success is counterbalanced by considerable treatment-related morbidity and mortality, with infectious complications standing as a primary cause of non-relapse mortality in this vulnerable population (3).

The profound immunosuppression induced by both the underlying hematologic malignancy and its intensive cytotoxic treatment creates a perfect storm for opportunistic infections (4). Chemotherapy-induced neutropenia, mucosal barrier injury, and the frequent use of indwelling central venous catheters collectively predispose children to a wide spectrum of bacterial, viral, and fungal pathogens (5). Among these infectious threats, pneumonia emerges as a particularly formidable adversary. It is a leading cause of febrile neutropenia episodes, hospital readmissions, delays in chemotherapy, and life-threatening sepsis in pediatric oncology patients (6). The clinical presentation can be atypical in neutropenic hosts, often lacking classic signs of consolidation, which complicates timely diagnosis and intervention (7). Moreover, the etiological spectrum is broad, encompassing typical community-acquired bacteria, opportunistic organisms like Pneumocystis jirovecii, and respiratory viruses, necessitating complex diagnostic and management strategies (8).

Despite its clinical significance, the precise burden of pneumonia in children undergoing treatment for acute leukemia, particularly within specific regional healthcare contexts, remains inadequately characterized (9). Epidemiological data on infection rates can vary considerably based on geographic location, local microbial ecology, hospital infection control practices, prophylactic antibiotic protocols, and the specific intensity of chemotherapeutic protocols employed (10). In Iran, and more specifically in the Northwest region, there is a paucity of recent, granular data detailing the incidence, risk factors, and outcomes of pneumonia in this pediatric subgroup (11). Existing studies from other parts of the country often focus on broader febrile neutropenia or aggregate infection data, without isolating pneumonia as a distinct clinical entity with unique diagnostic and therapeutic challenges (12).

Conducting a detailed assessment is crucial for several reasons. First, it establishes a local baseline epidemiology, which is essential for benchmarking care quality and informing empirical antibiotic guidelines. Second, identifying patterns such as seasonal variations, common causative agents (where diagnostics are available), and associations with specific phases of therapy can guide proactive preventive measures. Third, understanding the impact of pneumonia on clinical outcomes, including intensive care unit (ICU) admission rates, treatment delays, and mortality, highlights its contribution to the overall treatment burden and can justify resource allocation for advanced diagnostic tools or targeted prophylactic measures.

This study therefore aims to address this knowledge gap by conducting a retrospective analysis of the prevalence and clinical profile of pneumonia among children diagnosed with acute leukemia admitted to the oncology wards of teaching hospitals in Urmia, Iran, between 2020 and 2024. We seek to determine the frequency

of pneumonia episodes in relation to chemotherapy cycles, describe the diagnostic methods utilized, and analyze associated clinical outcomes. The findings from this investigation are expected to provide valuable evidence to optimize local clinical management protocols, enhance surveillance strategies, and ultimately contribute to reducing infection-related morbidity in children battling acute leukemia in our region.

2- MATERIALS AND METHODS

2-1. Study Design and Setting

A retrospective, cross-sectional study was conducted to investigate the prevalence and characteristics of pneumonia among children with ALL admitted to the oncology wards of two major university-affiliated teaching hospitals (Imam Khomeini Hospital and Motahari Hospital) in Urmia, Iran. These hospitals serve as the primary referral centers for pediatric oncology in West Azerbaijan province. The study period spanned from January 1, 2020, to December 31, 2023 (inclusive).

2-2. Study Population and Eligibility Criteria

The study population included all pediatric patients (aged ≤18 years) with a confirmed diagnosis of ALL who were admitted to the oncology wards during the study period.

Inclusion criteria

1. Age ≤ 18 years at the time of ALL diagnosis.
2. Confirmed diagnosis of ALL based on World Health Organization (WHO) classification, including morphological, immunophenotypic (flow cytometry), and cytogenetic/molecular assessments.
3. Receiving chemotherapy according to standard protocols (e.g., ALL IC-BFM 2009 or similar).
4. At least one episode of hospitalization during the study period for any reason (e.g., chemotherapy cycle, fever, complication management).

Exclusion criteria

1. Patients with incomplete or inaccessible medical records.
2. Patients with a concurrent diagnosis of another primary immunodeficiency disorder unrelated to leukemia or its treatment.
3. Episodes of pneumonia diagnosed within the first 72 hours of admission (to exclude community-acquired pneumonia present at the time of admission, focusing on healthcare-associated or treatment-related episodes). Patients with evidence of pulmonary metastasis from leukemia or other malignancies on imaging were also excluded.

2-3. Data Collection and Variables

Data were extracted from patients' electronic medical records and physical hospital charts using a standardized, pre-piloted data collection form. The data collection process was performed by two trained medical residents under the supervision of a pediatric oncologist. Any discrepancies were resolved by consensus or by consulting a third senior investigator.

The collected variables included:

1. ***Demographic and Clinical Data:*** Age at ALL diagnosis, sex, ALL risk stratification (standard, intermediate, high), phase of chemotherapy (induction, consolidation, interim maintenance, delayed intensification, maintenance), and date of ALL diagnosis, and nutritional status at diagnosis (assessed using body

mass index (BMI) z-scores calculated from weight and height, with underweight defined as BMI z-score < -2 standard deviations based on WHO growth charts).

2. ***Pneumonia Episodes:*** For each hospitalization, the presence of pneumonia was assessed. Pneumonia was defined as per the modified Centers for Disease Control and Prevention (CDC) criteria for healthcare-associated infections: the presence of new or progressive radiographic infiltrates on chest X-ray or CT scan plus at least two of the following clinical signs: (a) fever (>38.0°C) or hypothermia (<36.0°C), (b) new onset of cough or sputum production, (c) worsening respiratory symptoms (dyspnea, tachypnea), (d) leukocytosis, leukopenia, or left shift (13). All radiographs were reviewed by a pediatric radiologist blinded to the clinical details. To distinguish pneumonia from pulmonary leukemic infiltration (metastasis), we required that the radiographic infiltrates be new or progressive and associated with at least two clinical signs of infection, as per CDC criteria. Furthermore, patients with infiltrates that did not resolve with antibiotic therapy and had no microbiological confirmation, or those with known extramedullary disease, were carefully reviewed by the pediatric oncologist and radiologist to exclude leukemic infiltration.
3. ***Microbiological Data:*** Results of all microbiological investigations obtained within 48 hours of pneumonia diagnosis were recorded, including: blood cultures, sputum cultures (if obtainable), bronchoalveolar lavage (BAL) fluid cultures (if performed), and results of nasopharyngeal swabs for multiplex PCR panels (if available, e.g., for respiratory viruses like RSV, influenza, SARS-CoV-2). All blood culture samples were processed using the BACTEC FX automated continuous monitoring system (Becton Dickinson, USA). Serum galactomannan testing (Platelia Aspergillus EIA, Bio-Rad) was performed at the discretion of the treating physician for patients with suspected invasive fungal infection, and results were recorded when available. Routine screening for tuberculosis (TB) and non-tuberculous mycobacteria (NTM) was not part of the standard diagnostic workup; however, when clinically suspected (e.g., persistent fever, cavitary lesions, or lack of response to antibacterial therapy), acid-fast bacilli (AFB) smears, mycobacterial cultures, and/or TB PCR were performed, and these results were captured.
4. ***Treatment and Outcome Data:*** Empirical antibiotic regimen initiated, modifications based on culture results, need for ICU admission, need for and duration of mechanical ventilation, and outcome of the pneumonia episode (resolution, sequelae, death attributed to pneumonia).
5. ***Neutropenia Status:*** Absolute neutrophil count (ANC) at the time of pneumonia diagnosis was recorded. Severe neutropenia was defined as ANC < 500 cells/µL (14).

2-4. Operational Definitions

- ***Pneumonia Episode:*** An event meeting the clinical and radiological criteria mentioned above, separated from a previous

episode by a symptom-free interval of at least 14 days and/or a new radiological finding.

- ***Microbiologically Confirmed Pneumonia:*** A pneumonia episode with a confirmed pathogenic microorganism from a normally sterile site (e.g., blood) or a predominant organism from a lower respiratory tract sample (BAL). Cases with positive cultures for organisms considered contaminants (e.g., coagulase-negative staphylococci from a single blood culture, or normal respiratory flora from sputum without predominant growth) were not classified as microbiologically confirmed.
- ***Clinically Diagnosed Pneumonia:*** A pneumonia episode meeting clinical/radiological criteria but without a confirmed microbiological etiology.
- ***Pneumonia-Associated Mortality:*** Death occurring during the same hospitalization for pneumonia or directly attributable to its complications, as judged by the treating clinical team.

2-5. Sample Size and Sampling

A census sampling method was employed. All eligible patients admitted within the specified 4-year period were included in the initial screening.

2-6. Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp). Categorical variables (e.g., sex, pneumonia prevalence, microbiological etiology, mortality) were described using frequencies and percentages. Continuous variables (e.g., age, duration of hospitalization) were assessed for normality using the Kolmogorov-Smirnov test and described using mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate.

The primary outcome, the period prevalence of pneumonia, was calculated as: (Number of children with ALL who developed at least one episode of pneumonia during the study period / Total number of children with ALL admitted during the study period) × 100. The incidence density (episodes per 1000 patient-days) was also calculated. Associations between categorical variables (e.g., ALL risk group, chemotherapy phase, neutropenia status, underweight status) and the occurrence of pneumonia were assessed using the Chi-square test or Fisher's exact test. For continuous variables, the independent samples t-test or Mann-Whitney U test was used. A two-tailed p-value of <0.05 was considered statistically significant. Multivariable logistic regression analysis was planned to identify independent risk factors for developing pneumonia, including variables with a p-value <0.2 in the univariate analysis.

2-7. Ethical Considerations

Ethical approval for this study was obtained from the Ethics Committee of Urmia University of Medical Sciences (Approval Code: IR.UMSU.REC.1405.127). Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee. All methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

3-RESULTS

A total of 162 pediatric patients with confirmed ALL were admitted to the oncology wards during the study period (January 1, 2020, to December 31, 2023). After applying exclusion criteria, 150 patients were eligible for inclusion: 8 were excluded for incomplete medical records, 3

for concurrent primary immunodeficiency, 1 for pneumonia diagnosed within the first 72 hours of admission, and 1 for pulmonary leukemic infiltration (metastasis) without evidence of infection. The study cohort included 150 patients with a total of 1,250 hospitalizations and 18,750 patient-days of follow-up.

3-1. Demographic and Clinical Characteristics

The median age at ALL diagnosis was 6.5 years (IQR: 4.0–10.0), with a male predominance (58.0%). Most patients were classified as standard-risk ALL (52.0%), and the majority of hospitalizations occurred during the maintenance phase of chemotherapy (40.8% of episodes). Underweight status (BMI z-score < -2) was present in 24 patients (16.0%) at diagnosis. Among the 150 patients, 62 (41.3%) developed at least one episode of pneumonia during the study period, resulting in a period prevalence of 41.3% (95% CI: 33.5–49.1%). A total of 98 pneumonia episodes were identified across these patients, with an incidence density of 5.23 episodes per 1,000 patient-days (95% CI: 4.28–6.38). The distribution of pneumonia episodes by chemotherapy phase showed the highest occurrence during induction (32.7%) and maintenance (28.6%) phases. The demographic and clinical characteristics of the study population are summarized in Table 1.

Table-1. Demographic and clinical characteristics of pediatric patients with acute lymphoblastic leukemia (ALL) included in the study (N=150).

Characteristic	Total (N=150)	Patients with ≥1 Pneumonia Episode (n=62)	Patients without Pneumonia (n=88)	P-value*
Age at diagnosis, years Median (IQR)	6.5 (4.0–10.0)	5.8 (3.5–9.2)	7.0 (4.5–10.5)	0.12
Sex, n (%)				0.45
Male	87 (58.0)	38 (61.3)	49 (55.7)	
Female	63 (42.0)	24 (38.7)	39 (44.3)	
ALL risk stratification, n (%)				0.03
Standard	78 (52.0)	25 (40.3)	53 (60.2)	
Intermediate	45 (30.0)	20 (32.3)	25 (28.4)	
High	27 (18.0)	17 (27.4)	10 (11.4)	
Nutritional status, n (%)				0.03
Normal weight	126 (84.0)	47 (75.8)	79 (89.8)	
Underweight (BMI z < -2)	24 (16.0)	15 (24.2)	9 (10.2)	
Chemotherapy phase at hospitalization, n (%)†				<0.01
Induction	210 (16.8)	32 (32.7)	178 (14.9)	
Consolidation	180 (14.4)	18 (18.4)	162 (13.6)	
Interim maintenance	150 (12.0)	10 (10.2)	140 (11.7)	
Delayed intensification	210 (16.8)	10 (10.2)	200 (16.8)	
Maintenance	510 (40.8)	28 (28.6)	482 (40.4)	
Severe neutropenia (ANC <500 cells/µL) at hospitalization, n (%)†				<0.001
Yes	450 (36.0)	72 (73.5)	378 (31.7)	
No	800 (64.0)	26 (26.5)	774 (64.9)	

* P-values from Chi-square test or Fisher's exact test for categorical variables, and Mann-Whitney U test for continuous variables, comparing patients with and without pneumonia.

† Percentages based on total hospitalizations (N=1,250) or pneumonia episodes (n=98), as applicable.

- **IQR:** interquartile range; **ANC:** absolute neutrophil count.

Patients with pneumonia were more likely to have high-risk ALL (27.4% vs. 11.4%; P=0.03), underweight status (24.2% vs. 10.2%; P=0.03), and severe neutropenia during hospitalizations (73.5% of episodes vs. 31.7%; P<0.001). Pneumonia episodes were disproportionately associated with the induction phase (P<0.01).

3-2. Characteristics of Pneumonia Episodes

Details of the 98 pneumonia episodes are provided in Table 2. Most episodes (67.3%) were clinically diagnosed without microbiological confirmation, while 32.7% were microbiologically confirmed. Severe neutropenia was present in 73.5% of episodes. Radiographic findings primarily included bilateral infiltrates (55.1%) (Table 2).

The majority met multiple clinical criteria, with fever/hypothermia being the most common sign (93.9%).

3-3. Microbiological Etiologies

Microbiological data were available for 85 (86.7%) episodes. Among the 32 microbiologically confirmed cases, bacterial pathogens predominated (62.5%), followed by viral (25.0%) and fungal (12.5%). The most common isolates were Pseudomonas aeruginosa (25.0%) and respiratory syncytial virus (RSV) (12.5%). Details are shown in Table 3.

Of the 32 confirmed cases, 16 (50.0%) were diagnosed via blood culture (processed using the BACTEC FX system), 10 (31.3%) via BAL fluid culture, and 6 (18.8%) via nasopharyngeal swab PCR. Serum galactomannan was tested in 12 episodes, with 3 positive results (all in patients with Aspergillus culture). No cases of tuberculosis or non-tuberculous mycobacterial pneumonia were identified during the study period.

Table-2. Characteristics of pneumonia episodes in pediatric ALL patients (n=98 episodes).

Characteristic	n (%) or Median (IQR)
Type of pneumonia	
Clinically diagnosed	66 (67.3)
Microbiologically confirmed	32 (32.7)
Radiographic findings	
Unilateral infiltrates	28 (28.6)
Bilateral infiltrates	54 (55.1)
Other (e.g., consolidation, effusion)	16 (16.3)
Clinical signs (≥2 required)	
Fever/hypothermia	92 (93.9)
Cough/sputum production	78 (79.6)
Worsening respiratory symptoms	85 (86.7)
Leukocytosis/leukopenia/left shift	89 (90.8)
Neutropenia status	
Severe (ANC <500 cells/µL)	72 (73.5)
Non-severe	26 (26.5)
Chemotherapy phase	
Induction	32 (32.7)
Consolidation	18 (18.4)
Interim maintenance	10 (10.2)
Delayed intensification	10 (10.2)
Maintenance	28 (28.6)

Note : IQR: interquartile range; **ANC:** absolute neutrophil count.

Table-3. Microbiological etiologies of confirmed pneumonia episodes (n=32).

Pathogen Type and Isolate	n (%)
Bacterial	20 (62.5)
Pseudomonas aeruginosa	8 (25.0)
Klebsiella pneumoniae	5 (15.6)
Staphylococcus aureus	4 (12.5)
Other (e.g., Streptococcus pneumoniae)	3 (9.4)
Viral	8 (25.0)
Respiratory syncytial virus (RSV)	4 (12.5)
Influenza	2 (6.3)
SARS-CoV-2	2 (6.3)
Fungal	4 (12.5)
Aspergillus species	3 (9.4)
Candida species	1 (3.1)

3-4. Treatment and Outcomes

Empirical antibiotics were initiated in all episodes, most commonly with broad-spectrum agents (e.g., piperacillin-tazobactam plus vancomycin; 75.5%). Modifications occurred in 40.8% based on cultures. ICU admission was required in 22 (22.4%) episodes, with mechanical ventilation in 15 (15.3%; median duration 5 days, IQR: 3–8). Resolution occurred in 82 (83.7%) episodes, sequelae in 10 (10.2%), and pneumonia-associated mortality in 6 (6.1%). Mortality was higher in high-risk ALL patients (P=0.04).

3-5. Risk Factors for Pneumonia

Univariable analysis identified high-risk ALL (P=0.03), induction/maintenance chemotherapy phases (P<0.01), severe neutropenia (P<0.001), and underweight status (P=0.03) as associated with pneumonia. Multivariable logistic regression (Table 4) confirmed severe neutropenia (adjusted OR: 4.2, 95% CI: 2.1–8.4; P<0.001) and high-risk ALL (adjusted OR: 2.8, 95% CI: 1.3–6.0; P=0.009) as independent risk factors, whereas underweight status did not remain significant (adjusted OR: 1.7, 95% CI: 0.8–3.6; P=0.15) (Table4).

4- DISCUSSION

This retrospective study provides a detailed analysis of the prevalence, characteristics, and outcomes of pneumonia in children with ALL treated at teaching hospitals in Urmia, Iran, between 2020 and 2023. The key findings reveal a substantial burden of pneumonia in this population, with a period prevalence of 41.3% and an incidence density of 5.23 episodes per 1000 patient-days. Severe neutropenia and high-risk ALL were identified as independent risk factors for developing pneumonia. While most episodes were managed successfully, a notable proportion led to severe outcomes, including ICU admission and pneumonia-associated mortality.

Table-4. Multivariable logistic regression analysis of risk factors for developing pneumonia in pediatric ALL patients (N=150).

Variable	Adjusted OR (95% CI)	P-value
High-risk ALL (vs. standard)	2.8 (1.3–6.0)	0.009
Severe neutropenia (yes vs. no)	4.2 (2.1–8.4)	<0.001
Induction phase (vs. maintenance)	1.9 (0.9–4.0)	0.09
Underweight (vs. normal weight)	1.7 (0.8–3.6)	0.15

Note : OR: odds ratio; **CI:** confidence interval.
Model adjusted for variables with P<0.2 in univariable analysis
(age, risk stratification, chemotherapy phase, neutropenia).

The high prevalence of pneumonia observed in our cohort aligns with the established vulnerability of pediatric leukemia patients to severe infections due to treatment-induced immunosuppression (15, 16). Our reported prevalence of 41.3% is consistent with studies from other regions, though direct comparisons are challenging due to variations in study design, definitions of pneumonia, and local epidemiological and clinical practices (17). For instance, a study from a tertiary center in Turkey reported a similar incidence of lower respiratory tract infections in pediatric oncology patients (18). The incidence density of 5.23 episodes per 1000 patient-days underscores the frequency of this complication within the high-risk inpatient setting, highlighting the constant threat infections pose to treatment continuity and patient safety.

The distribution of pneumonia episodes across chemotherapy phases offers critical insights into periods of heightened vulnerability. The highest proportion of episodes occurred during the induction phase, a finding consistent with global literature (19, 20). Induction chemotherapy is the most intensive phase, causing profound and prolonged neutropenia and mucosal damage, which drastically increases susceptibility to bacterial and fungal pathogens. The second peak during the maintenance phase, though less intuitively obvious, is also documented. During maintenance, although chemotherapy is less intensive, the cumulative immunosuppression, prolonged duration of treatment, and increased community exposure (as children are often managed as outpatients) may explain this pattern, particularly for viral pathogens (21, 22). This bimodal risk distribution necessitates tailored preventive strategies, strict neutropenia management and anti-bacterial/anti-fungal prophylaxis during induction, and emphasis on viral prevention (e.g., vaccination, isolation precautions) during maintenance.

The role of nutritional status in infection risk is an important consideration. In our study, underweight patients had a higher unadjusted risk of pneumonia, but this association did not persist after adjusting for neutropenia and ALL risk group. This suggests that malnutrition may exert its effect primarily through its well-known contribution to impaired immune function and myelosuppression, rather than as an independent factor. Nonetheless, ensuring adequate nutritional support remains a cornerstone of supportive care, as it may indirectly reduce infection risk by improving immune competence and treatment tolerance.

Our microbiological findings, while limited by a high rate of clinically diagnosed episodes, reflect the challenges of etiological diagnosis in neutropenic patients. The predominance of bacterial pathogens, with Pseudomonas aeruginosa and Klebsiella pneumoniae as leading isolates, is consistent with patterns in febrile neutropenia (23, 24). This supports the continued use of broad-spectrum anti-pseudomonal agents as empirical therapy in our setting. The significant proportion of viral and fungal causes underscores the importance of a comprehensive diagnostic approach beyond bacterial cultures. The detection of respiratory viruses like RSV and influenza highlights the need for robust infection control measures and seasonal prophylaxis in oncology wards. The presence of Aspergillus species, though less frequent, is concerning given its association with high mortality, suggesting that a low threshold for advanced imaging and biomarker testing (e.g., galactomannan) is warranted in high-risk patients with persistent fever (25). The use of the BACTEC FX system for blood cultures likely enhanced our yield for bacterial pathogens, though the retrospective nature of the study meant that

not all patients underwent all available diagnostic tests. Importantly, we did not identify any cases of tuberculosis or non-tuberculous mycobacterial pneumonia in our cohort, which may reflect the low local prevalence or the fact that these are not routinely sought without strong clinical suspicion.

The identification of severe neutropenia (ANC <500 cells/μL) as the strongest independent risk factor for pneumonia is biologically plausible and reinforces a central tenet of supportive care in oncology (26). This finding emphasizes the critical importance of meticulous monitoring of blood counts, timely administration of granulocyte colony-stimulating factors (G-CSF) as per protocol, and aggressive management of febrile neutropenia. Furthermore, the association between high-risk ALL and increased pneumonia risk likely reflects the more intensive chemotherapy regimens used for this subgroup, leading to deeper and more prolonged immunosuppression (27). These patients represent a target population for enhanced surveillance and potentially more aggressive prophylactic strategies.

4-1. Proposed Prevention Algorithm

Based on our findings and current international guidelines, we propose a risk-stratified prevention algorithm for pneumonia in pediatric ALL patients:

1. Risk Stratification at Diagnosis:

- High-risk: High-risk ALL (as per protocol), severe neutropenia expected (>7 days), prior pneumonia, or underweight status.
- Standard-risk: All other patients.

2. High-Risk Patients:

- Induction/Consolidation Phases:
  - Antibacterial prophylaxis: Fluoroquinolone (e.g., levofloxacin) during expected neutropenia >7 days (per institutional protocol and resistance patterns).
  - Antifungal prophylaxis: Mould-active azole (e.g., voriconazole or posaconazole) during prolonged neutropenia or if on intensive chemotherapy.
  - Anti-PJP prophylaxis: Co-trimoxazole as per ALL protocol.
  - Nutritional support: Aggressive nutritional intervention with dietitian consultation and supplementation to maintain BMI z-score ≥ -2.
  - Monitoring: Twice-weekly ANC monitoring; daily clinical assessment for respiratory symptoms.
  - Vaccination: Annual influenza vaccine (and COVID-19 boosters) for patient and household contacts; RSV prophylaxis (palivizumab) in eligible infants.
- Maintenance Phase:
  - Emphasis on viral prevention: Hand hygiene, mask-wearing during community outbreaks, isolation of symptomatic contacts.
  - Continue anti-PJP prophylaxis per protocol.
  - Low threshold for chest imaging and diagnostic workup for any respiratory symptom.

3. Standard-Risk Patients:

- Adhere to standard ALL protocol prophylaxis (e.g., co-trimoxazole).
- Encourage vaccination and nutritional optimization.

- Prompt evaluation of fever or respiratory symptoms, with escalation to a high-risk protocol if severe neutropenia develops.

The clinical outcomes observed in this study illuminate the significant morbidity associated with pneumonia in this population. The requirement for ICU admission in nearly one-quarter of episodes and mechanical ventilation in 15.3% signifies the potential for rapid clinical deterioration. The pneumonia-associated mortality rate of 6.1% is a sobering reminder that infections remain a leading cause of non-relapse mortality, even in the era of modern supportive care (28). The higher mortality observed in patients with high-risk ALL further underscores their vulnerability. These outcomes translate into substantial healthcare costs, treatment delays, and psychological distress for patients and families, justifying investments in preventive measures.

4-2. Limitations

This study has several limitations inherent to its retrospective design. First, the reliance on medical records may have led to incomplete data capture, particularly regarding subtle clinical signs or microbiological tests not routinely performed. The high rate of clinically diagnosed pneumonia reflects real-world diagnostic challenges but limits etiological conclusions. For instance, galactomannan testing was not universally performed, and mycobacterial screening was only done on clinical suspicion, potentially underestimating fungal or mycobacterial etiologies. Second, the single-center (two-hospital) design may limit the generalizability of our findings to other regions in Iran or countries with different antimicrobial resistance patterns, infection control protocols, or chemotherapeutic regimens. Third, the study period included the COVID-19 pandemic, which may have influenced hospitalization patterns, infection control practices, and the prevalence of specific pathogens like SARS-CoV-2, though our data showed only two such cases. Finally, we could not analyze the impact of specific prophylactic antimicrobials (e.g., co-trimoxazole for PJP, antivirals) due to inconsistent documentation, which is an important area for future research. Finally, while we carefully distinguished pneumonia from pulmonary leukemic infiltration using clinical and radiological criteria, the lack of biopsy in most cases means that some misclassification cannot be entirely ruled out.

4-3. Research Implications

Despite these limitations, our findings have important implications for clinical practice and health policy in our region. They strongly advocate for:

1. Strengthening Diagnostic Capacity: Increasing access to rapid molecular diagnostics for respiratory viruses and fungal biomarkers could reduce the proportion of empirically treated cases and allow for targeted therapy.

2. Enhancing Prophylaxis Protocols: The data support rigorous application of antibacterial, antifungal (especially during high-risk phases), and anti-PJP prophylaxis according to international guidelines. Vaccination strategies for influenza and COVID-19 for patients and caregivers should be optimized.

3. Risk-Stratified Management: Patients with high-risk ALL and those with severe neutropenia should be recognized as priority groups for closer monitoring and aggressive empirical treatment at the first sign of infection.

4. Infection Control Reinforcement: Strict adherence to hand hygiene, isolation protocols for patients with respiratory symptoms, and minimizing ward traffic are essential, particularly during community viral outbreaks.

5- CONCLUSION

In conclusion, this study demonstrates that pneumonia is a frequent and serious complication in children undergoing treatment for ALL in Urmia, Iran, with a prevalence exceeding 40%. The risk is significantly heightened during periods of severe neutropenia and in patients with high-risk disease. While bacterial infections are common, viral and fungal etiologies contribute substantially to the disease burden, necessitating a broad diagnostic and therapeutic approach. The associated rates of ICU admission and mortality highlight the critical need for optimized preventive strategies, vigilant monitoring, and prompt management. Future prospective studies incorporating advanced microbiological techniques and evaluating the effectiveness of specific prophylactic interventions are warranted to further reduce the burden of pneumonia in this vulnerable population.

6- CONFLICT OF INTERESTS

The authors have declared that they have no competing interests.

7- FUNDING

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8- REFERENCES

1. Liu CY, Li C. Clinical features and risk factors of severe pneumonia in children with acute lymphoblastic leukemia. Frontiers in Pediatrics. 2022 May 6;10:813638.

2. Yin T, Han J, Hao J, Yu H, Qiu Y, Xu J, et al. Clinical characteristics and risk factors of acute lymphoblastic leukemia in children with severe infection during maintenance treatment. Cancer Medicine. 2023 Oct;12(19):19372-82.

3. Karadoğan M, Mutlu FT. Analyse of febrile neutropenia attacks in children with acute lymphoblastic leukemia: febrile neutropenia with acute lymphoblastic leukemia. The Journal of Pediatric Academy. 2023 Aug 10;4(3):81-6.

4. Susanah S, Alam A. Risk factors associated with sepsis in children with acute lymphoblastic leukemia and febrile neutropenia. Paediatrica Indonesiana. 2024 Jun 14;64(3):270-6.

5. Šegulja S, Vranešević K, Đorđević A, Roganović J. Infections in children with acute lymphoblastic leukemia. Medicina. 2024 Aug 26;60(9):1395.

6. Nair A, Elballushi R, Joshi R, Anjanappa S, Akter M, Arif S, et al. Assessment of the prevalence of infections in pediatric patients with acute lymphoblastic leukemia. Cureus. 2023 Oct 11;15(10).

7. Patel PA, DeGroote NP, Jackson K, Cash T, Castellino SM, Jaggi P, et al. Infectious events in pediatric patients with acute lymphoblastic leukemia/lymphoma undergoing evaluation for fever without severe neutropenia. Cancer. 2022 Dec 1;128(23):4129-38.

8. Sharma N, Jamwal M, Digra S, Parihar R, Gupta N. Evaluation of febrile neutropenia in diagnosed cases of acute lymphoblastic leukemia in children. IP Innovative Publication. 2024;14(3):686-90.

9. Iqbal L, Riaz S, Gull S, Iqbal I, Gull A, Ahmed T. 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. 2025 Jul 31:112-7.

10. Ciesielska M, Orzechowska B, Gamian A, Kazanowska B. Epidemiology of childhood acute leukemias. Postępy Higieny i Medycyny Doświadczalnej. 2024 Jan 1;78(1):22-36.

11. Delkhah M, Arasteh J, Koochakzadeh L, Rostami S. Evaluatin of Association of rs4986790 and rs4986791 SingleNucleotide Polymorphisms in TLR4 with Febrile Neutropenia in Childhood Acute Lymphoblastic Leukemia.

12. Kalicińska E, Jabłonowska-Babij P, Morawska M, Iskierka-Jażdżewska E, Drozd-Sokołowska J, Paszkiewicz-Kozik E, et al. RETRACTED: Pneumonia in Patients with Chronic Lymphocytic Leukemia Treated with Venetoclax-Based Regimens: A Real-World Analysis of the Polish Adult Leukemia Group (PALG). Cancers. 2024 Dec 13;16(24):4168.

13. DEBNATH A, BATABYAL S, TAPADAR SR, CHAUDHURI AD. Comparison between the Clinical Pulmonary Infection Score and Modified Centre for Disease Control Criteria for Diagnosis of Ventilator-associated Pneumonia: A Cross-sectional Study. Journal of Clinical & Diagnostic Research. 2025 Jun 1;19(6).

14. Murakami Y, Shindo Y, Sano M, Okumura J, Kobayashi H, Sakakibara T, et al. Effects of lymphocyte and neutrophil counts and their time courses on mortality in patients with postoperative pneumonia. Scientific Reports. 2022 Aug 26;12(1):14564.

15. Bochennek K, Hogardt M, Lehrnbecher T. Immune signatures, testing, and management of febrile neutropenia in pediatric cancer patients. Expert Review of Clinical Immunology. 2023 Mar 4;19(3):267-77.

16. Zhang Y, Sun L, Li X, Zhang R, Liu J, Li J. Risk factors and clinical management strategies for bloodstream infections in pediatric hematological malignancies. Risk Management and Healthcare Policy. 2025 Dec 31:3303-10.

17. Kyriakidis I, Mantadakis E, Stiakaki E, Groll AH, Tragiannidis A. Infectious complications of targeted therapies in children with leukemias and lymphomas. Cancers. 2022 Oct 14;14(20):5022.

18. Sezgin Evim M, Tüfekçi Ö, Baytan B, Ören H, Çelebi S, Ener B, et al. Invasive Fungal Infections in Children with Leukemia: The Clinical Features and Prognosis. Turkish journal of haematology: official journal of Turkish Society of Haematology. 2022;39.

19. Zajac-Spychala O, Kampmeier S, Lehrnbecher T, Groll AH. Infectious complications in paediatric haematopoetic cell transplantation for acute lymphoblastic leukemia: current status. Frontiers in pediatrics. 2022 Feb 10;9:782530.

20. Rodriguez PR, Mehta D, Subhan M, Yadav RP, Yousofzai BS, Al-Najjar EH, et al. Evolving horizons in pediatric leukemia: novel insights, challenges, and the journey ahead. Cureus. 2024 Aug 22;16(8).

21. Dunn KA, MacDonald T, Rodrigues GJ, Forbrigger Z, Bielawski JP, Langille MG, et al. Antibiotic and antifungal use in pediatric leukemia and lymphoma patients are associated with increasing opportunistic pathogens and decreasing bacteria responsible for activities that enhance colonic defense. Frontiers in cellular and infection microbiology. 2022 Jul 27;12:924707.

22. Carlesse F, de Sousa AV. Infections in children and adolescents with acute leukemia. EJC Paediatric Oncology. 2024 Jun 1;3:100142.

23. Iftekhar A, Zafar A, Zeeshan M, Sheikh U, Fadoo Z, Waqas S, et al. Descriptive analysis of frequency and antimicrobial susceptibility of pathogens isolated from acute leukemia patients with febrile neutropenia over a four-year period at a tertiary hospital. BMC Infectious Diseases. 2026 Mar 2;26(1):730.

24. Mattei D, Baretta V, Mazzariol A, Maccacaro L, Balter R, Zaccaron A, et al. Characteristics and outcomes of

bloodstream infections in a tertiary-care pediatric hematology–oncology unit: a 10-year study. Journal of Clinical Medicine. 2022 Feb 8;11(3):880.

25. Zaj N, Kopyt W, Kamizela E, Zarychta J, Kowalczyk A, Lejman M, et al. Diagnostic and Therapeutic Challenge Caused by Candida albicans and Aspergillus spp. Infections in a Pediatric Patient as a Complication of Acute Lymphoblastic Leukemia Treatment: A Case Report and Literature Review. Pathogens. 2024 Sep 7;13(9):772.

26. Boeriu E, Borda A, Vulcanescu DD, Sarbu V, Arghirescu ST, Ciorica O, et al. Diagnosis and management of febrile neutropenia in pediatric oncology patients—a systematic review. Diagnostics. 2022 Jul 25;12(8):1800.

27. Leardini D, Muratore E, Abram N, Baccelli F, Belotti T, Prete A, et al. Effectiveness of quinolone prophylaxis in pediatric acute leukemia and hematopoietic stem cell transplantation: a systematic review and meta-analysis. InOpen forum infectious diseases 2022 Dec 1 (Vol. 9, No. 12, p. ofac594). US: Oxford University Press.

28. Singer CE, Popescu AI, Văruț RM, Popescu M, Loredana D, Radivojevic K, et al. Bacterial Pathogen Profiles and Antibiotic Resistance in Pediatric Leukemia Patients: Insights for Optimizing Infection Management in Immunocompromised Children. Antibiotics. 2024 Dec 22;13(12):1234.