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Lower Respiratory Infections in Children With Febrile Neutropenic Leukemia: A Case in a Jordanian Hospital

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Abstract

The study aimed to examine the prevalence of pneumonia in pediatric children diagnosed with leukemia at King Hussein Medical Center, Royal Medical Services, Amman, Jordan. The study was conducted from January 2019 to March 2020. A total of 100 hospitalized leukemia patients with febrile neutropenic episodes were evaluated for the presence of pneumonia. Samples were collected from all patients and tested for microbial growth. Univariate analysis revealed that age ($P = .033$) and packed cell volume ($P = .006$) were statistically significant risk factors, associated with the prevalence of pneumonia in leukemia patients with febrile neutropenia episodes. Similarly, as the absolute neutrophil count counts increased with an odds ratio and a 95% confidence interval of 2.386 (0.859-6.625), the odds of pneumonia in febrile neutropenic patients were more prevalent. The study reported the prevalence of pneumonia in immunocompromised febrile neutropenic patients with leukemia, which could lead to the development of evidence-based febrile neutropenic treatment protocol development. It will assure more responsive patient management and treatment.

Keywords

febrile neutropenia, chemotherapy, pediatric, leukemia, Jordan

Introduction

Leukemia is a malignant neoplastic disease, commonly found in pediatric patients and accounts for one third of childhood malignancies.[1] Fever is the most common complication of neutropenic patients and is associated with nonmalignant mortality and morbidity.[2] Respiratory infections are a recurrent source of fever in neutropenic patients with high mortality and morbidity rates. Among these patients, fungal and bacterial agents are common causes of lower-respiratory-tract infections.[3,4] On the contrary, the occurrence of influenza infection with a high fatality rate is likely to be reported in neutropenic patients. In addition, a precise clinical presentation of a viral infection is not always recorded in neutropenic patients.[5,6] Viruses such as herpes virus and cytomegalovirus are identified as the cause of posttransplant fever in patients going through stem cell transplant (SCT).[7-10]

One of the approved treatment methods for leukemia, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), comprises chemotherapy. Patients on chemotherapy repeatedly suffer low immune function and subsequent exposure to infection. One of the most common complications of infection is pneumonia.[11] The reports suggest that 13% to 31% of leukemic children are on chemotherapy, and more than 80% of SCT recipients experienced pneumonia episodes at least once.[12,13] Pneumonia attributes to 25% to 80% of case fatalities among leukemic patients.[14] In leukemia patients, a more prominent complication associated with pneumonia is the presence of neutropenia. The dose-dependent reduction in the neutrophil count during leukemia occurs due to the sensitivity of neutrophils toward nucleoside analogs and alkylating agents. Severe neutropenia involves a drop in absolute neutrophil count (ANC) to less than 500/μL with the presence of lung

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Table 1. Definitions of Terminologies Used for the Enrolled Febrile Neutropenic Patients With Lower-Respiratory-Tract Infection.

Terminologies	Definitions
Fever	Defined as a single axillary temperature of 38.3°C or above 38.0°C persistent for over 1 hour
Febrile neutropenia	Presence of axillary temperature equal to 38.3°C or above 38.0°C persistent for 1 hour and an absolute neutrophil count (ANC) of less than 500/μL presenting neutropenia
Neutropenic episode	One episode is considered as time from patient hospitalization with febrile neutropenia and treatment with antibiotics leading to fever being resolved but neutropenia persists till the reoccurrence of fever
Afebrile state	Recovery from the febrile neutropenia episode with ANC count more than 1000/μL and no fever
Pneumonia	Presence of fever and respiratory symptoms and the detection of new infiltrates presence on chest x-rays and positive blood culture

infection caused by fungi or bacteria.[15] The risk of development of infection in the pediatric population with febrile neutropenia (FN) differs. Among the pediatric population, 33% to 50% of all FN episodes indicate a lower risk of severe infection complication.[16,17]

Approximately 44% of FN in leukemic children are classified as respiratory viral infections in a prospective multicenter study.[1] However, most of the existing information has been derived from studies that assessed adult patients with cancer or transplant recipients concerning the clinical course of respiratory viral infections. Studies that explained the epidemiology of lower-respiratory-tract infection, particularly pneumonia among the pediatric population, during leukemia treatment are limited. Therefore, this study aims to study the prevalence of pneumonia in pediatric patients diagnosed with leukemia during admission and hospitalization in King Hussein Medical Center, Royal Medical Services, Amman, Jordan.

Material and Methods

This prospective epidemiologic analytical study was conducted at Queen Rania Al-Abdullah Hospital for children located at King Hussein Medical Center from January 2019 to March 2020 among leukemia patients to examine the prevalence of pneumonia during admission and hospitalization.

The study included patients diagnosed with leukemia including "ALL and AML" aged from 1 to 15 years, with the presence of FN and consistent fever after 4 days of antibiotic initiation. Patients with all other cancers were excluded. The study commenced after the collection of informed consent for enrolled leukemic children from their respective parents or guardians. Patients' detailed medical history including baseline investigations and chest x-rays was collected. All laboratory values were obtained from enrolled patients at the time of admission. The study used a FN protocol as followed by clinicians at Queen Rania Al-Abdullah Hospital and the management of febrile neutropenic episodes. Moreover, lower-respiratory-tract infections were dependent on the clinician's choice of treatment. Chest x-rays were performed for all enrolled patients to determine the presence of lower-respiratory-tract infections. The definition and reference range for fever, FN, febrile neutropenic episode, afebrile state, and pneumonia as major lower-respiratory-tract findings are explained in Table 1.

Patients were enrolled and had a chest computed tomography scan in cases of worsening respiratory symptoms, abnormal chest x-ray, or fungal infection with a strong clinical suspicion on paranasal sinus x-ray including clinically evident sinusitis, nonresponsive fever, throat ulceration, or oral ulceration. A review of the microbiology records in the Princess Oman Center for Laboratory Research was performed. All positive blood cultures for patients were recorded. In case of symptoms worsening or lack of response to antibiotics, urine culture, Bactec blood culture, and galactomannan antigen testing were repeated.

Procedure for Blood Culture Sampling for Detection of Potential Infectious Etiology

Data related to microbial identification and susceptibility patterns were gathered. All blood samples were collected at the bedside by using an aseptic technique. The skin was disinfected with 70% isopropyl alcohol, followed by 2% iodine tincture. After injecting the blood culture bottles with the drawn blood, labeled bottles were sent to the microbiology department for incubation in 1 of 3 different detection systems (Versa Trek, Bactec, and Bact alert, (Biomerieus, USA) for up to 5 days, following the guidelines of the bottle manufacturer.

The bottles flagged as positive were evaluated with the Gram staining technique to examine the type of microorganism. Afterward, each bottle was subcultured on blood if gram-positive microbes were observed and on Cystine lactose electrolyte deficient media (CLED) agar if gram-negative microbes were observed and

Table 2. The Inclusion Criteria for Patient Enrollment, Baseline Reports, Management, and Antibiotic Profile Used in the Treatment of Enrolled Patients.

Inclusion criteria	Age between 1 and 15 years
	Diagnosed cases of ALL and AML
	Presence of febrile neutropenia and consistent fever after 4 days of antibiotic initiation
Baseline reports	Baseline laboratory examination
	Radiographic images
	Medical history and physical examination
Management protocol	Blood and urine cultures were performed for febrile neutropenic patients
	Bactec blood culture and galactomannan antigen testing
	Initiation of empiric antibiotics
Mono/dual or triple therapies	Third-generation antibiotics (cephalosporins)
	Addition of antifungal (amphotericin B)
	Addition of aminoglycosides or an antipseudomonal agent
	Addition of aminoglycosides or antipseudomonal agents and anti-gram-positive agents (cloxacillin, vancomycin)
	Other combination therapies
	ALL chemotherapy protocol
	AML chemotherapy protocol

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

incubated for 24 to 48 hours at 37°C. Furthermore, it may be subcultured on sabouroud agar if fungal microbes were noted. The isolates obtained from cultures were marked for identification by using "Vitek 2 ID cards," with the capability to identify different microorganisms including fungal microorganisms. In addition, susceptibility testing for antibiotics was done using "Vitek 2 AST cards" by Vitek 2 compact system according to the recommendation of Clinical and laboratory standard institute (CLSI).

Management Protocol and Antimicrobial Profile

The management and treatment protocols followed in this study have been shown in Table 2. Broad-spectrum antibiotics were started empirically in febrile neutropenic patients including cephalosporins and aminoglycosides. In cases suspected of pneumonia, anti-gram-positive agents were incorporated into the protocol. The adjustment in the treatment protocol was made by clinicians as per the culture report of the individual patient. The antifungal drug amphotericin B was used as empirical therapy for persistent fever after 96 hours with or without pneumonia or in case of suspected fungal infection.

Statistical Analysis

Statistical analysis was performed using descriptive statistics. Mean and standard deviation (SD) were calculated. For quantitative variables and qualitative variables, frequency (percentage) was provided. The odds ratio (OR) was calculated using a 95% confidence interval (CI) through binary logistic regression. *P* values were calculated for all variables, and a *P* value $<.05$ was considered statistically significant. *T*-test and chi-square test were used in analytical statistics by SPSS version 25 software (SPSS version 25, Chicago, Illinois).

Results

In this study, 100 patients were enrolled from January 2019 to March 2020 with a mean ($\pm$SD) age of 9.7 ($\pm$5.03) years. Of all patients, 53.3% were male, and 60% were diagnosed with AML. Overall, 15 (15%) febrile neutropenic patients developed pneumonia during admission and treatment as the most prevalent lower-respiratory-tract infection, followed by (14%) Viridans Streptococcus and (14%) *Staphylococcus aureus*. One hundred forty-three FN episodes were observed in 100 enrolled leukemic patients. Fifty-six patients were reported with a single febrile neutropenic episode, and 44 patients reported 2 or more FN episodes with a mean episode per patient of 1.43. Eight (53.3%) male and 7 (46.7%) female patients developed lower-respiratory-tract infections. Out of 15 febrile neutropenic patients that developed pneumonia, 9 (60%) patients were diagnosed with ALL, while 4 (26.7%) patients had AML. No bone marrow transplant nor Down syndrome history was reported among enrolled patients. A peripheral intravenous device was used in 10 (66.7%) patients, while a port-a-cath device was used for 2 (13.3%), and a Hickman line was passed in 2 (13.3%) patients. Out of

Table 3. Characteristics of Study Population.

Variable	Pneumonia		Total
	Yes ($n = 15$)	No ($n = 85$)	
Gender n (%)			
Male	8 (53.3)	43 (50.6)	51 (51)
Female	7 (46.7)	42 (49.4)	49 (49)
Age (years) (mean ± SD)	9.7 ± 5.03	6.5 ± 3.96	7.05 ± 4.25
Leukemia type, *n* (%)			
Acute lymphoblastic leukemia	9 (60)	69 (81.2)	78 (78)
Acute myeloid leukemia	4 (26.7)	13 (15.3)	17 (17)
Relapse	2 (13.3)	3 (3.5)	5 (5)
Central line ($n = 94$), *n* (%)			
Peripheral	10 (66.7)	59 (69.4)	69 (69.0)
Stem cell transplantation	—	—	—
Down syndrome	—	—	—
Port-a-cath	2 (13.3)	13 (15.3)	15 (15.0)
Hickman	3 (20)	7 (8.2)	10 (10.0)
Remission status ($n = 96$), *n* (%)			
In remission	7 (47)	58 (68.2)	65 (65.0)
Not in remission	8 (53)	27(31.8)	35 (35)
Blood culture, *n* (%)			
Central	11 (73.3)	70 (82.4)	81 (81.0)
Peripheral	4 (26.7)	15 (17.6)	19 (19.0)
Positive blood cultures, *n* (%)			
Streptococcus pneumoniae	15 (15)	—	—
Candida spp.	—	13 (15.2)	—
Staphylococcus aureus	—	14 (16.4)	—
Escherichia coli	—	13 (15.2)	—
Klebsiella species	—	12 (14.1)	—
Viridans Streptococcus	—	14 (16.4)	
Coagulase-negative staphylococci	—	10 (11.7)	
Others	—	9 (10.5)	—
Laboratory values with reference range (mean ± SD)			
WBC (mean ± SD) (RR: 4000-10000 cm)	3.0 ± 2.80	6.69 ± 30.94	6.13 ± 28.55
PCV (mean ± SD) (RR: 39%-49.5%)	31.6 ± 3.64	29.9 ± 4.93	30.2 ±4.78
PLT (mean ± SD) (RR: 150-410 × 10^9/L)	179.93 ± 395	170.60 ± 156.989	172 ± 207.5
ANC (mean ± SD) (RR: 1.8-8 × 10^3 cells/μL)	0.54 ± 0.623	1.50 ± 2.77	1.36 ± 2.58
ESR (mean ± SD) (RR: 0-15 mm/1st hour, for male) (RR: 0-20 mm/1st hour, female)	55.47 ± 24.56	52.28 ± 23.32	52.76 ± 23.4

Abbreviations: SD, standard deviation; ANC, absolute neutrophil count; RR, reference range; PLT, platelet count; WBC, white blood cells; PCV, packed cell volume; ESR, erythrocyte sedimentation rate.

15 neutropenic patients, 7 (47%) patients were in the leukemia remission phase. However, 8 (53%) patients were not in the remission phase. Central blood culture was detected in 73.3% of the patients, while 26.7% of the patients were found to have a positive peripheral blood culture. Laboratory investigation of enrolled subjects with pneumonia showed a mean (±SD) white blood cell count of 3.0 (±2.80), packed cell volume (PCV) 31.6 ± 3.64, platelet count of 179.93 ± 395, ANC of 0.54 ± 0.623, and erythrocyte sedimentation rate 55.47 ± 24.56. Radiological sinusitis was observed in 4 febrile neutropenic patients. The percentage of positive blood cultures included 15% for *Streptococcus pneumoniae*, 15.2% for Candida species, and 16.4% for *Staphylococcus aureus*. The clinical and demographic profiles of enrolled patients are displayed in Table 3.

Binary logistic regression and univariate analysis were performed for identifying the prevalence of pneumonia in leukemia patients (Table 4) to study the association of study variables with disease outcome. Based on the findings, age ($P = .033$) and PCV ($P = .006$) were found to be statistically significant risk factors

Table 4. Association of Study Variables With Disease Outcome by Applying Binary Logistic Regression.

Variables	*P* value	Exp(B) (odds ratio)	95% CI for Exp(B)	
			Lower	Upper
Age	.033	.800	.652	.983
Gender				
Female		1		
Male[a]	.879	.890	.199	3.983
Leukemia type				
ALL[a]		1		
AML	.781	.412	.187	2.567
Relapse	.070	.314	.089	1.099
Central line				
Peripheral[a]				
Port-a-cath	.878	1.012	.345	2.765
Hickman	.958	1.022	.453	2.307
WBC	.448	1.130	.824	1.551
PCV	.006	.725	.577	.910
PLT	.108	.997	.994	1.001
ANC	.095	2.386	.859	6.625
ESR	.848	1.003	.974	1.033
Remission status				
In remission[a]				
Not in remission	.694	.917	.595	1.413
Blood culture				
Central[a]				
Peripheral	.203	.302	.048	1.906

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; WBC, white blood cells; PCV, packed cell volume; PLT, platelet count; ANC, absolute neutrophil count; ESR, erythrocyte sedimentation rate.
[a]Reference category.

associated with the prevalence of pneumonia in leukemia patients with FN episodes. Similarly, as the ANC counts increase with an OR and a 95% CI of 2.386 (0.859-6.625), the odds of getting pneumonia in febrile neutropenic patients are frequent (Table 3).

Table 5 shows the multivariate analysis of patients with the first febrile neutropenic episode, considered as the reference group. The OR was obtained for the remaining 2 groups including FN at the time of admission and during hospitalization in comparison to patients with the first febrile episode. The results showed higher odds of getting pneumonia in patients with FN during hospitalization (OR = 7.41, 95% CI: 5.98-10.47).

Discussion

Pneumonia is a prevalent health issue that leads to mortality and morbidity and is a burden on health care resources. This prospective epidemiologic analytical study of pneumonia in leukemia patients reveals that out of 100 children, pneumonia was detected in 15 children; 9 (60%) patients with ALL, 4 (26.7%) patients with AML, and 2 (13.3) children with relapse. These findings correlate to those of the study by Garcia et al[13] which revealed a high percentage of pneumonia syndrome reported in patients with ALL, AML, and high-risk Myelodysplastic syndromes (MDS). In this study, AML was the second-highest recurrent type of leukemia. A total of 66.7% of children were treated with peripheral devices, followed by (20%) Hickman and port-a-cath (13.3%) devices. Relapse is considered a major issue as it lowers the survival rate of leukemic children. A study on substantial childhood leukemia indicated that relapse rates vary between 12% and 20%.[18,19] In the current study, relapse occurred in 6.7% of the patients having remission, low overall 5-year survival, and high mortality rates. Previous studies conducted in Mexico and Pakistan have revealed similar findings.[20-22] These studies reported relapse rates of 21.5%, 26.2%, and 58.5%, respectively. Similarly, another study conducted in Saudi Arabia reported a low 5-year overall survival and relapse rate of 15.1%.[23] Similarly, our study reported age as a significant risk factor associated with the prevalence of pneumonia. Another study reported the highest incidence of invasive pneumococcal disease among geriatrics followed by children aged <2 years.[24] A study in the Philippines reported age (2-5 months) as a risk factor for fatal pneumonia outcomes in the pediatric population and was significantly associated with death.[25] Lower immunoglobin G levels in blood and lack of fully functional immune systems in infants, in comparison to older age groups, could be the influencing factors for higher risk in the age group of 2 to 5 months.[26,27] The present study also reported PCV as an associated risk factor for pneumonia in leukemia patients. However, further studies are required to further explore this risk factor among different pediatric populations.

Although such findings are advantageous, it is vital to identify the limitations of this study for a better understanding of the outcomes of this study. In the first place, the detection of pneumonia is complicated to be established with certainty in this population.[28] Due to the increased capillary permeability, many of the likely manifestations of pneumonia, which include drug toxicity, hydrostatic pulmonary edema, leukemic infiltrates, and pulmonary edema, might have contributed to misclassification. A definition of pneumonia based on predefined guidelines was used for minimizing the likelihood of this outcome. A standardized approach for ruling out alternative radiographic infiltrating causes was adopted.

Table 5. Factors Associated With Febrile Neutropenia at the Time of Admission and During Hospitalization on Multivariate Analysis.

	FN at admission		FN during hospitalization	
Variables	Odds ratio	95% Confidence interval		Odds ratio
Gender				
Male	1		Male	1
Female	0.94	0.68-1.32	Female	0.94
Leukemia type				
Acute lymphoblastic leukemia	1		Acute lymphoblastic leukemia	1
Acute myeloid leukemia	0.13	2.61-3.27	Acute myeloid leukemia	0.13
Pneumonia	2.19	1.74-2.54	**Pneumonia**	2.19
Fungal infections	1.85	1.47-2.01	**Fungal infections**	1.85
Bacterial infections	0.87	0.87-1.03	**Bacterial infections**	0.87

Abbreviation: FN, febrile neutropenia.

A possible pathogen was identified in 1 of the cases. This finding is corroborated by the conclusions of previous literature.[29-31] In addition, the strong association of neutropenia to pneumonia suggests that most of these events were certainly infectious as neutropenia cannot be a risk factor for hydrostatic pulmonary edema or drug toxicity. In addition, persistent misclassification bias may remain, and under this condition, the bias will be higher, which will result in an inaccurately high estimation of pneumonia. Notably, some of these relationships might not be causal. Other outcomes should be considered preliminary such as the relationship between low baseline platelet count and a higher risk of pneumonia. Probably, severe thrombocytopenia is just an indicator of additionally profound marrow involvement by leukemia, which results in higher infection rates. On the contrary, recent work recommends that platelets have an essential function in immune response and inflammation.

Moreover, this was a single-center study; thus, it focused only on inpatients. Therefore, the findings may not be generalizable to other settings. Particularly, the occurrence of pneumonia reduced in leukemia patients undergoing outpatient induction as compared with the population investigated. The occurrence of pneumonia was similar to other centers without clarity regarding whether the population comprises inpatients and outpatients.[32,33]

In conclusion, this study has identified pneumonia as a risk factor in leukemia patients as it was found to be common with ALL and AML patients. Antiviral therapies, active and passive immune prevention approaches, molecular diagnostic techniques, and respiratory viral infections remain a significant burden for leukemic children despite advanced AML treatment strategies. More importantly, with the use of empiric therapy, neutropenic pneumonia fatality rates remain increased in patients. However, expanding the use of modern molecular techniques, including galactomannan testing, facilitates fungal pathogen identification, which contributes to pneumonia severity in febrile neutropenic leukemia patients.[34] Controlled surveys are required to study whether mild febrile respiratory infections in leukemic children could be managed irrespective of antibiotics.

Conclusion

The study reported the prevalence of pneumonia in immunocompromised febrile neutropenic patients with leukemia. The primary diagnosis was abnormal chest x-ray and radiographic sinusitis as predictors of pneumonia. It is due to bacterial or invasive fungal infection that led to the development of evidence-based febrile neutropenic treatment protocols to assure more responsive patient management and treatment.

Authors' Note

The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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Author Contributions

Nimer, N. substantially contributed to design, conception, analysis and interpretation of data and drafting the article,

Khader, M., Oudat, R.,Hazaima, R. and Alkaabna, A. contributed to acquisition and interpretation of data and the final approval of the version to be published.

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