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Original research

ASSESSMENT OF INFECTION RATE DURING THE INDUCTION PHASE IN ACUTE LEUKEMIA PATIENTS

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ABSTRACT

Introduction: *Acute leukemia is the most common cancer in children, and infections is one of the major complications during treatment. This study aimed to assess the incidence of infections during the induction phase of acute leukemia treatment.*

Methods: *A cross-sectional descriptive study of the clinical and paraclinical characteristics of acute leukemia in children. And a longitudinal follow-up study of infectious diseases during the induction treatment phase between December 2022 and July 2024 at the Pediatric Center, Hue Central Hospital. Data were extracted from medical records and analyzed using SPSS v.18.0 (IBM Corp., Armonk, NY, USA).*

Results: *A total of 55 patients with acute leukemia were included in the study, comprising 13 cases of acute myeloid leukemia (AML), 29 cases of high-risk acute lymphoblastic leukemia (HR-ALL), and 13 cases of standard-risk acute lymphoblastic leukemia (SR-ALL). Infections occurred in 85.5% of patients during the induction phase, with the highest incidence observed in the first three weeks of treatment (95.7%). Patients with AML had a significantly higher infection rate compared to those with ALL (92.3% vs. 83.3%, $p < 0.01$). The most common site of infection was the oropharynx (29.8%), followed by the gastrointestinal tract (27.7%), lower respiratory tract (23.4%), and bloodstream (sepsis) (21.3%). Urinary tract infections were the least common (2.1%). Additionally, 21.3% of patients experienced infections involving two or more organ systems. The rate of positive blood cultures was 17.0%, while positive fungal cultures accounted for 4.2%. The success rate of infection treatment was 89.4%, with a mortality rate of 10.6%.*

Conclusions: *Infections are highly prevalent during the induction phase of acute leukemia treatment. Early detection and prompt administration of antibiotics are critical to managing infections and improving patient outcomes.*

Keywords: *Acute myeloid leukemia; Acute lymphoblastic leukemia, children, infection.*

I. INTRODUCTION

Acute leukemia is the most common type of malignancy in children, accounting for approximately 25% of newly diagnosed childhood cancers. Among these, lymphoblastic leukemia accounts for 75%, acute myeloid leukemia for 20%, and the remainder are other rarer forms [1-3].

In the 1960s, the survival rate for acute leukemia was very low, less than 10%. However, with advancements in modern medicine, survival rates have significantly improved. In particular, the survival rate for patients with acute lymphoblastic leukemia has reached over 90% in developed countries [4, 5].

Despite this progress, infectious complications remain the leading cause of morbidity and mortality in children with malignancies [6, 7]. Infections not only increase the risk of death but also prolong hospitalization, delay chemotherapy treatment, impair quality of life, and increase the use of healthcare resources [8].

At the Pediatrics Department of Hue Central Hospital, approximately 30 new cases of acute

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leukemia are diagnosed and treated each year. To contribute to understanding the clinical and paraclinical characteristics as well as to provide further information about infectious complications during the induction treatment phase of acute leukemia in children, thereby improving survival rates, we conducted this study to describe the characteristics of acute leukemia in children; and to describe common infections occurring during the induction treatment phase of acute leukemia in children.

II. MATERIAL AND METHODS

Study design includes two studies: A cross-sectional descriptive study of the clinical and paraclinical characteristics of acute lymphoblastic and myeloid leukemia in children. And a longitudinal follow-up study of infectious diseases during the induction treatment phase at Pediatric Center, Hue Central Hospital, Vietnam.

Inclusion criteria were as follows: patients were newly diagnosed with acute leukemia [9, 10] and treated at Pediatric Center between April 2022 and July 2024, and followed protocol treatment of Hue Central Hospital for each kind of acute leukemia [11-13], those aged < 16 years old.

Exclusion criteria were as follows: pediatric patients with secondary or relapsed acute leukemia; patients with pre-existing infections prior to induction therapy according to the treatment protocol, and cases where the child and the representative did not agree to participate in the study.

Data collection procedures: Demographic, clinical and laboratory variables were abstracted from electronic medical records on a pre-piloted case-record form. Daily bedside reviews captured febrile episodes, culture results, antimicrobial therapy and clinical response until completion of induction or death.

Outcome measures: Primary outcome - cumulative incidence of any infection during induction. Secondary outcomes - distribution of infection sites/pathogens, timing relative to chemotherapy week, association with neutrophil count, and infection-attributable mortality.

Statistical analysis: Data were entered into SPSS v18.0 (IBM, Armonk, NY). Categorical variables are presented as frequencies/percentages and compared using chi-square or Fisher's exact tests. Continuous variables are summarised with median (IQR) or mean ± SD and compared by Mann-Whitney U or Student's t-test as appropriate. Two-sided $p < 0.05$ denoted statistical significance.

III. RESULTS

A total of 55 patients were included during the study period. The proportion of male and female were 54.5% and 45.5% respectively, resulting in a male-to-female ratio of 1.2:1. The 1 - < 5 years age group accounted for the highest proportion (45.4%), while the < 1 year age group had the lowest (1.8%). The median age was 5 years.

The proportion of patients living in rural areas was higher than those in urban areas (76.4% vs. 23.6%). There were no statistically significant differences in gender, age, or residential location between the two leukemia subtypes ($p > 0.05$).

Among the study population, 23.6% were diagnosed with acute myeloid leukemia (AML), while acute lymphoblastic leukemia (ALL) was more prevalent, accounting for 76.4%. Of those with acute lymphoblastic leukemia, 69.0% were classified as high risk, and 31.0% as standard risk.

The most common reasons for hospital admission among the study population were fever (63.6%), pallor (54.5%), bleeding (30.9%), fatigue (25.5%), lymphadenopathy (16.4%), bone and joint pain (12.7%), cough (12.7%), and vomiting (10.7%). Symptoms such as weight loss, abdominal pain, and headache were less frequently observed.

The median white blood cell (WBC) count at admission was 21.1×10^9/l, and the median neutrophil count was 1.5×10^9/l. The mean hemoglobin level at admission was 8.0 ± 2.3 g/dl, and the median platelet count was 34.0×10^9/l. Thus, the median neutrophil count, platelet count, and mean hemoglobin level were all lower-than-normal reference values at the time of hospital admission.

There were no statistically significant differences in WBC count, neutrophil count, hemoglobin level, or platelet count at admission between the two leukemia subtypes ($p > 0.05$).

Regarding blast cells, the group with ≥ 60% peripheral blood blasts at admission accounted for the highest proportion (34.5%), while the group with 40 - 60% blasts had the lowest proportion (10.9%). The median percentage of peripheral

blood blasts at admission was 35%. There was no statistically significant difference in peripheral blast counts at admission between the two leukemia subtypes ($p > 0.05$).

The majority of patients (85.5%) had elevated lactate dehydrogenase (LDH) levels. The median LDH level was 611 U/L. There was no statistically significant ($p > 0.05$). Similarly, the majority of patients in the study had a cerebrospinal fluid (CSF) white blood cell (WBC) count < 5 cells/mm³, accounting for 98.2%. Only 1 patient (1.8%) had an elevated CSF WBC count of ≥ 5 cells/mm³.

The infection rate during the induction treatment phase was 47 out of 55 patients (85.5%). Among them, patients with acute myeloid leukemia (AML) and high-risk acute lymphoblastic leukemia (ALL) had a higher risk of infection, accounting for 92.3% and 96.6%, respectively, compared to 53.8% in the standard-risk ALL group. This difference was statistically significant ($p < 0.05$) (see Table 1).

Table 1: The distribution of infection status by leukemia subtype during the induction phase

Disease group	Infection					p
	Total	Yes		No		
	n	n	%	n	%	
Acute myeloid leukemia	13	12	92.3	1	7.7	0.002
Acute lymphoblastic leukemia, HR	29	28	96.6	1	3.4	
Acute lymphoblastic leukemia, SR	13	7	53.8	6	46.2	
Total	55	47	85.5	8	14.5	

The most common type of infection was oral and pharyngeal infection, accounting for 29.8%, followed by gastrointestinal infections (27.7%), lower respiratory tract infections (23.4%), and sepsis (21.3%). The least common infections were urinary tract infections and viral infections, each accounting for 2.1%.

The rate of sepsis among patients with acute lymphoblastic leukemia (ALL) was higher than in those with acute myeloid leukemia (AML) (28.6% vs. 0%). In contrast, gastrointestinal infections were more common in patients with AML compared to those with ALL (58.3% vs. 17.1%). These differences were statistically significant ($p < 0.05$).

There were no statistically significant differences between the two leukemia subtypes regarding the rates of lower respiratory tract infections, oral-pharyngeal infections, urinary tract infections, skin and soft tissue infections, varicella virus infections, and infections with unknown focus ($p > 0.05$) (see Table 2).

Table 2: Sites of infection occurring during the induction phase

Site of infection	Total		ALL		AML		p
	n	%	n	%	n	%	
Sepsis	10	21.3	10	28.6	0	0	0.046
Lower respiratory tract infection	11	23.4	10	28.6	1	8.3	> 0.05
Oral and pharyngeal infection	14	29.8	12	34.3	2	16.7	> 0.05
Gastrointestinal infection	13	27.7	6	17.1	7	58.3	0.010
Urinary tract infections	1	2.1	1	2.9	0	0	> 0.05
Skin and soft tissue infections	3	6.4	2	5.7	1	8.3	> 0.05
Varicella virus infections	1	2.1	1	2.9	0	0	> 0.05
Infections with unknown focus	12	25.5	9	25.7	3	25.0	> 0.05

Regarding the common types of infections that occur during the induction treatment phase were described in the table 3. They included gastroenteritis (23.4%), pneumonia (23.4%), sepsis (21.3%), ulcerative gingivitis (17%), bronchitis (8.5%), pharyngitis (6.4%), tonsillitis (6.4%), and several other infections, each accounting for less than 5%. In 25.5% of cases, the infection focus could not be identified.

Table 3: Types of Infections during Induction treatment by Leukemia subtype

Type of infection		Total		ALL		AML	
		n	%	n	%	n	%
Sepsis		10	21.3	10	28.6	0	0
Lower respiratory tract infection	Pneumonia	11	23.4	10	28.6	1	8.3
Oral and pharyngeal infection	Ulcerative gingivitis	8	17.0	7	20.0	1	8.3
	Pharyngitis	3	6.4	3	8.6	0	0
	Tonsillitis	3	6.4	2	5.7	1	8.3
	Oral fungal	2	4.3	2	5.7	0	0
Gastrointestinal infection	Gastroenteritis	11	23.4	5	14.3	6	50.0
	Hepatosplenic fungal	1	2.1	1	2.9	0	0
	Necrotizing enterocolitis	1	2.1	0	0	1	8.3
Urinary tract infections	Lower urinary tract infection	1	2.1	1	2.9	0	0
Skin and soft tissue infections	Perianal abscess	1	2.1	1	2.9	0	0
	Injection site infection	1	2.1	0	0	1	8.3
	Skin ulcer on forearm	1	2.1	1	2.9	0	0
Virus infection	Varicella virus	1	2.1	1	2.9	0	0
Infection with unknow focus		12	25.5	9	25.7	3	25.0

Regarding the causative agents of infection, the majority of patients had clinically diagnosed infections (83%), while bacterial infections with confirmed microbiological evidence accounted for 17%, and fungal infections made up 4.2%.

The proportion of patients with infection in a single organ/system was the highest (63.8%), followed by those with infections in 2-3 organ systems (19.2%), and the lowest was in those with infections in more than 3 organ systems (2.1%). Most infections occurred during the first three weeks of the treatment protocol, with the highest incidence in week 2 (40.4%), followed by week 1 (36.2%), and the lowest in week 4 (4.3%). There was a correlation between infection status and neutrophil count. Infections were most frequent (49.2%) in patients with an absolute neutrophil count (ANC) $\leq 0.1 \times 10^9$/L, and least frequent (23.1%) in those with an ANC $> 0.5 \times 10^9$/L.

Regarding treatment response, the majority of patients (91.7%) achieved remission after the induction phase of acute leukemia treatment, while 8.3% died following treatment (Table 4).

Table 4: Infection response outcomes during the induction phase

Treatment outcome	Total		ALL		AML	
	n	%	n	%	n	%
Recover	42	89.4	31	88.6	11	91.7
Death	5	10.6	4	11.4	1	8.3
Total	47	100.0	35	100.0	12	100.0

IV. DISCUSSION

Our results showed that 47 out of 55 patients (85.5%) developed infections during the induction treatment phase. The infection rate in patients with acute myeloid leukemia (AML) was 92.3%, higher than that in acute lymphoblastic leukemia (ALL) patients, where 35 out of 42 children (83.3%) developed infections. Among the ALL group, the high-risk subgroup had an infection rate of 96.6%, which was significantly higher than the standard-risk subgroup, at 53.8%. This difference was statistically significant ($p < 0.05$). Our study is consistent with the findings of Trần Thu Thuỷ (2014), which reported that during the induction chemotherapy phase, infectious complications occurred in 235 out of 270 children (87%) with acute leukemia, including 92.0% in acute myeloid leukemia (AML) and 83.5% in acute lymphoblastic leukemia (ALL), with a statistically significant difference ($p < 0.05$) [14]. In a multicenter study on sepsis following chemotherapy in pediatric ALL patients in China (2020), it was found that the intermediate/high-risk group had a significantly higher rate of sepsis compared to the low-risk group (17.1% vs. 9.1%, $p < 0.001$). The induction phase was identified as the period during which most sepsis episodes occurred - 66.8% in the low-risk group and 56.1% in the intermediate/high-risk group [15]. The infection rate in AML patients was higher than in ALL patients, possibly because myeloid-directed chemotherapy regimens cause deeper marrow suppression, and the infiltrative nature of myeloid blasts is more aggressive than that of lymphoid blasts, resulting in more severe neutropenia and a higher risk of infection. Infections remain a common cause of treatment-related mortality in children with acute leukemia. Induction chemotherapy often leads to profound and prolonged neutropenia, increasing susceptibility to infections. Infections can progress rapidly, requiring prompt recognition and management.

Regarding the site of infection during the induction treatment phase, oral and pharyngeal infections were the most common, accounting for 29.8%, followed by gastrointestinal infections (27.7%), infections of unknown focus (25.5%), lower respiratory tract infections (23.4%), and sepsis (21.3%), while urinary tract infections were less common, at 2.1%. These findings are consistent with those reported by Rajeswari Binitha [16], Sayed H.A[17], and Trần Thị Thu Thủy [14]. Chemotherapy is one of the main causes of mucosal damage, targeting all rapidly dividing and continuously renewing cells such as cancer cells, gastrointestinal mucosa, and oropharyngeal epithelial cells which allows bacteria to gain access to the bloodstream. Therefore, the most frequently observed clinical manifestations in patients undergoing chemotherapy are oral-pharyngeal and gastrointestinal infections. In some cases, infection may present only as febrile neutropenia. During this period of immunosuppression, patients may lack the ability to localize the infection, which prevents the development of typical clinical signs, leading to a relatively high proportion of infections with no identifiable focus. And our study showed that infections were most common when the absolute neutrophil count (ANC) was $\leq 0.1 \times 10^9$/L, accounting for 49.2% of cases. This is consistent with the findings of Trần Thu Thuỷ [14], McKormic [18], which demonstrated that the lower the ANC, the higher the risk of infection, particularly severe infections.

And there was a statistically significant difference in the rate of sepsis, with a higher incidence in acute lymphoblastic leukemia (ALL) compared to acute

myeloid leukemia (AML) (28.6% vs. 0%, p = 0.046 < 0.05). However, this finding may be influenced by our limited sample size, as only 13 out of 55 patients in our study had AML, and no cases of sepsis were recorded in this group. This result differs from other studies on AML, which have shown that intensive chemotherapy regimens often lead to profound and prolonged neutropenia, making children more susceptible to infections, especially sepsis [19].

According to our study, among the 47 pediatric patients who developed infections during the induction treatment phase, 8 cases (17%) had confirmed bacterial pathogens, and 2 patients (4.2%) tested positive for fungal cultures. The remaining 83% were diagnosed with clinically suspected infections without microbiological evidence. In the study by Meir Hadir M et al. (2001), infections were microbiologically documented in 59% (n = 137) of febrile neutropenia episodes. In 96 episodes (41%), there was no clinical or microbiological evidence of infection, and the fever was classified as of unknown origin [20]. Compared to that, the rate of pathogen isolation in our study was relatively low, possibly due to limitations in specimen collection techniques or bacterial culture procedures. Additionally, the majority of patients received broad-spectrum antibiotics prior to culture, which may have contributed to the low rate of positive culture results in our study.

Our results showed that during treatment, 63.8% of pediatric patients had infections involving a single organ, 19.2% had infections involving 2-3 organs, and 2.1% had infections involving more than 3 organs. In 14.9% of cases, the site of infection was unclear. Comparing with Thuy's research, among all pediatric patients with infections, single-organ infections accounted for 29.4%, infections involving two organs for 11.9%, three organs for 10.6%, and infections with unidentified focus had the highest proportion at 48.1% [14]. Table 4 shows that the response to antibiotics in our study resulted in recovery from infection in 89.4% of patients, while the mortality rate was 10.6% which was higher than the result of Bakhshi, 13 children (4.9%) died during the induction and consolidation phases, and all deaths were infection-related [21]. These findings indicate that infection is the leading cause of mortality during chemotherapy in children with acute leukemia.

V. CONCLUSION

During chemotherapy for pediatric patients with acute leukemia, infectious complications are almost inevitable. However, the ability to promptly detect and appropriately treat infections, including the judicious use of antibiotics, is critically important, not only to save the child's life but also to limit the emergence of antibiotic resistance in the community as well as in hospital.

Ethical approval

This study was approved by the Hue Central Hospital Ethics Committee in 2022. Consent was obtained from all participants' parents or guardians in this study.

Conflict of Interest

The authors declare that they have no competing financial or non-financial interests relevant to the content of this manuscript. All authors have read and approved the final version, and they alone are responsible for its accuracy and integrity.

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