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Original Article

Risk factors associated with sepsis in children with acute lymphoblastic leukemia and febrile neutropenia

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Abstract

Background Children with acute lymphoblastic leukemia (ALL), especially those with febrile neutropenia, are susceptible to sepsis. Several factors have been associated with the occurrence of sepsis in children with leukemia.

Objective To identify potential risk factors associated with sepsis in children with ALL and febrile neutropenia.

Methods This cross-sectional study was done in children with ALL who sought treatment at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia from January 2019 to March 2022. We recorded patients' gender, age, nutritional status, absolute neutrophil count (ANC), co-infection, prophylactic antibiotic use, and phase of chemotherapy.

Results Of 131 subjects, 57.3% were male and 42.8% were wasted. Subjects had a median age of six years old and median ANC of 230 cells/mm^3. Furthermore, 48.9% of subjects had co-infections, 87.8% had not received prophylactic antibiotics, and 48.9% were in the induction phase of chemotherapy. Multiple logistic regression analysis revealed that older age [OR 1.16 (95%CI 1.04 to 1.29); β=0.149; P=0.008] and co-infection [OR 12.9 (95%CI 5.01 to 33.21); β=2.551; P<0.001] were significantly associated with sepsis in children with ALL and febrile neutropenia. Bronchopneumonia was the most common co-infection (72.5%).

Conclusion Older age and co-infection are significantly associated with sepsis in children with ALL and febrile neutropenia. **[Paediatr Indones. 2024;64:270-6; DOI: 10.14238/pi64.3.2024.270-6].**

Keywords: *ALL; children; febrile neutropenia; sepsis*

Acute lymphoblastic leukemia (ALL) is the most common cancer in children, accounting for 20% of all cancer cases before the age of 20.[1,2] Patients with ALL are more susceptible to invasive infections due to several factors, including ulcerated lesions on the mucosal surface as well as immunocompromised state caused by chemotherapy, radiation, immune-modulating treatments, and/or the disease itself.[3] Systemic infections vary and are influenced by clinical variables which lead to varying degrees of sepsis severity. An immunocompromised condition has been associated with decreased sepsis survival, and neutropenia has been associated with an increased risk of sepsis-related critical illness.[4] A study in El Salvador reported that 18.7% of leukemic children with febrile neutropenia developed sepsis, with a mortality rate of 2.9%.[3] The incidence rate of documented septicemia in ALL children in China was 12.9%.[3] Febrile neutropenia, associated with sepsis development, is an emergency condition defined as an axillary temperature of >38°C on one measurement

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or >37.5°C for at least one hour in patients with an absolute neutrophil count (ANC) of <500/mm^3 or between 500 and 1000/mm^3 and whose ANC was expected to decrease below 500/mm^3 in 24 to 48 hours.[5]

Several factors have been found to be associated with sepsis development in children with ALL and febrile neutropenia, including female gender, age of over 10 years, malnutrition, low ANC, presence of co-infections, absence of prophylactic antibiotic use, and chemotherapy regimens causing myelosuppressive conditions.[6-9] A previous study concluded that many pathogens have higher susceptibility in males rather than females.[7] However, no study has specifically assessed the association between such factors with sepsis in children with ALL and febrile neutropenia. In the present study, we aim to assess the associations of potential risk factors, including gender, age, nutritional status, ANC, co-infections, prophylactic antibiotic use, and chemotherapy regimen, with sepsis in children with ALL and febrile neutropenia.

Methods

This cross-sectional study was conducted at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. We included children with ALL who were treated and hospitalized between January 2019 and March 2022 with an ANC of <1,500 cells/mm^3 and a temperature of >38°C. Patients who met the inclusion criteria were recruited until the required sample size was obtained. Patients with incomplete medical record data were excluded. The variables assessed were gender, age, nutritional status, ANC, co-infections, prophylactic antibiotic use, chemotherapy regimens, and sepsis.

Nutritional status was classified as normal, moderately wasted, severely wasted, and overnourished based on z-scores on the *World Health Organization* (WHO) weight-for-height (or weight-for-length) growth charts.[10] Normal was defined as a Z-score <2 and >-2. Moderately wasted was defined as a Z-score ≤−2 and ≥−3. Severely wasted was defined as Z-scores <-3. Overweight and obese were grouped as overnourished, it was defined as a Z-score >2. Moderately wasted and severely wasted are further labeled as nutritional status 1 and nutritional status 2 in statistical analysis, respectively.

Co-infection was defined as a recent secondary infection occurring during febrile neutropenia which was not observed on admission, while febrile neutropenia was defined as ANC below 1,500 cells/mm^3 with temperature above 38°C. An infection type was defined as a single case of an infection of the patient during the current period. Chemotherapy phase was defined as the patient's most recent chemotherapy phase on hospital admission and classified as induction, consolidation, re-induction, or maintenance phase; patients who had not received chemotherapy were classified as such. Sepsis was defined as hypotension requiring vasopressor therapy to maintain mean arterial pressure >65 mmHg and serum lactate levels >2 mmol/L after management of hypovolemia. In the acute setting, we screened for sepsis in acutely ill, high-risk patients as a standard operating procedure, using the Sepsis-related Organ Failure Assessment (SOFA) score.[11]

We presented categorical data as frequencies and percentages and numerical data as medians and ranges. The univariate and multivariate analyses were carried out using simple and multiple logistic regression tests, respectively. The variables that turned out to be significant for sepsis after univariate analysis were then included in multivariate analysis to explore independent risk factors for sepsis. A P value of <0.05 was considered statistically significant.

This study was approved by the Ethics and Research Committee (ERC) of Dr. Hasan Sadikin General Hospital. Written approval was obtained from the hospital authorities before data collection. Written informed consent was sought from the parents of all participants.

Results

From January 2019 to March 2022, a total of 131 subjects were included, 48 with sepsis and 83 without sepsis. Characteristics of subjects are presented in **Table 1**.

Median age of subjects was 6 (range 1-16) years. Slightly more subjects were males (57.3%) than females (42.7%). Among the subjects, a majority fell under the normal category (55%), followed by wasted (42.8%). High-risk ALL was the most common type of leukemia (58.8%). Sepsis was observed in

Table 1. Subject characteristics (N=131)

Characteristics	N (%)
Sex	
Male	75 (57.3)
Female	56 (42.7)
Median age (range), years	6 (1-16)
Nutritional status	
Normal	72 (55.0)
Moderately wasted	31 (23.7)
Severely wasted	25 (19.1)
Overnourished	3 (2.3)
ALL classification	
HR-ALL	77 (58.8)
SR-ALL	54 (41.2)
Sepsis	
Yes	8 (36.6)
No	83 (63.4)
Median length of hospitalization (range), days	48 (1-54)
Median duration of fever (range), days	8 (3-120)
Median ANC (range), cells/mm3	230 (0-1,500)
Chemotherapy phase, n (%)	
Not given	30 (22.9)
Induction	64 (48.9)
Consolidation	11 (8.4)
Re-induction	7 (5.3)
Maintenance	19 (14.5)
Co-infection	
Yes	64 (48.9)
No	67 (51.1)
Prophylactic antibiotic use	
Yes	16 (12.2)
No	115 (87.8)

ALL=acute lymphoblastic leukemia; HR=high risk; SR=standard risk; ANC=absolute neutrophil count

approximately one-third of patients (36.6%). Median length of hospitalization was 8 (range 1-54) days, while median duration of fever was 8 (range 3-120) days. Median ANC was 230 (range 0-1,500) cells/mm^3.

The associations between sepsis and clinical characteristics of children with ALL and febrile neutropenia are presented in **Table 2**. Univariate analysis using simple logistic regression revealed that among the characteristics tested, older age, and the presence of a co-infection had significant associations with sepsis (P=0.008 and P<0.001, respectively).

There was no significant difference found in the proportion of sex between the groups with and without sepsis (P=0.483). Older age was significantly associated with a higher sepsis incidence rate (P<0.05). Almost half of the children in the sepsis group were severely wasted (45.8%), but the nutritional status was not significantly different between groups (P=0.191). The difference in ANC among children with and without sepsis was not significant (P=0.327). Meanwhile, the presence of co-infection was significantly associated with sepsis (P<0.001). Bronchopneumonia was the most common infection type in 72.5% of patients with sepsis in ALL patients with febrile neutropenia. There was no significant difference between groups given antibiotic prophylactic and not (P=0.681) even though the majority of the children with sepsis were given one. Furthermore, 50% of them were in the induction phase, but this, too, was not significantly different (P=0.704).

From the multiple logistic regression analysis, both the age (P=0014) and the presence of co-infection (P<0.001) were shown to be significant and independently associated with sepsis in ALL patients

Table 2. Univariate analysis of clinical characteristics and sepsis in children with ALL with febrile neutropenia

Characteristics	Sepsis		P value
	Yes (n=48)	No (n=83)	
Gender, n(%)			0.483
Male	26 (54.21)	49 (59.0)	
Female	22 (45.8)	34 (40.9)	
Median age (range), years	7 (2-15)	5 (1-16)	0.008
Nutritional status, n(%)			0.191
Normal	25 (52.1)	47 (56.6)	
Moderately wasted	12 (25)	13 (15.6)	
Severely wasted	10 (20.8)	21 (25.3)	
Overnourished	1 (2.1)	2 (2.4)	
Median length of hospitalization (range), days	12 (3-120)	13.44 (3-90)	0.952
Median duration of fever (range), days	11 (1-54)	8.31 (4-33)	0.327
Median ANC (range), cell/mm^3	180 (0-1500)	280 (0-1500)	0.704
Chemotherapy regimens, n(%)			0.645
Induction	24 (50)	40 (48.2)	
Consolidation	6 (12.5)	9 (10.8)	
Re-induction	0	3 (3.6)	
Maintenance	6 (12.5)	13 (15.5)	
Not given	12 (25)	18 (21.4)	
Co-infection, n(%)			0.645
No	8 (16.7)	59 (71.1)	
Yes	40 (83.3)	24 (28.9)	
Number of infection type			<0.001
Bronchopneumonia	29 (72.5)	7 (29.16)	
Urinary tract infection	3 (7.5)	-	
Gastroenteritis	6 (15)	8 (33.33)	
Otitis media	1 (2.5)	-	
SSTI	8 (20)	3 (12.5)	
Mucositis	2 (5)	3 (12.5)	
Bloodstream infection	17 (42.5)	6 (25)	
Prophylactic antibiotic use, n(%)			0.681
Yes	5 (10.4)	11 (13.3)	
No	43 (89.6)	72 (86.7)	

ANC=absolute neutrophil count

Table 3. Multiple logistic regression analysis

Effect	β	SE	Wald	Adj OR (95%CI)	P value
Age	0.149	0.056	7.102	1.16 (1.04 to 1.29)	0.008
Co-infection (yes *vs.* no)	2.557	0.482	28.106	12.90 (5.01 to 33.21)	<0.001

β=regression coefficient; SE=standard error; OR=odds ratio; CI=confidence interval

with febrile neutropenia, with an OR of 1.16 (95%CI 1.04 to 1.29; P=0.008) for age and 12.9 (95%CI 5.01 to 33.21; P<0.001) for co-infection (**Table 3**).

Discussion

Age and co-infection were significantly associated with sepsis. The risk of sepsis increased along with age (β=0.123; P=0.008). A previous study has validated three independent variables which were detected within 24 hours of hospital admission and associated with sepsis in pediatric cancer patients with febrile neutropenia: age ≥12 years, serum C-reactive protein (CRP) ≥90 mg/L, and interleukin-8 (IL-8) ≥300 pg/mL.[8] This finding was consistent with our results, in

which older children were at higher risk of infection, possibly due to the myelosuppressive chemotherapy regimen given to the high-risk group, which included subjects above 10 years of age.[4]

The majority of our subjects were male, as were more than half of the subjects with sepsis. This finding was in agreement with previous studies, which found that most children with sepsis and ALL were male.[6,12] Yet, there was no significant association with sepsis in our ALL and febrile neutropenia patients.[12] The similar findings were found in previous studies. However, a previous study demonstrated that sex steroid hormone, as in male and female patients, might bring different responses to infection.[12] Testosterone in males has an immunosuppressive effect in reducing interferon (IFN) and reducing interleukin-4 secretion in T cells. Moreover, estrogen in females can increase Th1 cellular immune response at low doses, and enhance Th2 response and humoral immunity at higher concentrations.[7] Nonetheless, there were no consistent differences found in sepsis outcomes to gender.

Almost half of the sepsis group was in normal nutritional status, and there was no significant difference in nutritional status between those with and without sepsis. This is different from a previous study in Indonesia that noted an increased risk of neutropenia by 1.25 times in malnourished patients.[6] The risk of infection has been theorized to increase malnourishment due to impairments in the immune system, intestinal barrier, and granulocyte activity.[9,13] In this study, the insignificance was likely due to the low number of subjects in each category.

Absolute neutrophil count also had no significant association with the incidence of sepsis in children with ALL and febrile neutropenia ($P=0.327$), but the sepsis group had a lower median ANC level (180 cell/mm^3 *vs.* 280 cell/mm^3, respectively). Past studies have stated that neutropenia is a major risk factor for infection in the blood in patients with leukemia. Neutropenia in patients receiving cytotoxic therapy for cancer has generally been associated with life-threatening opportunistic disease. A study found that more than 80% of cases of sepsis were associated with neutropenia in people receiving cytotoxic therapy.[14] Another study stated that bacteremia occurred in 10-25% of patients with leukemia, and mostly in those with profound febrile neutropenia.[15]

Co-infection had a significant association with sepsis in our subjects ($P<0.001$). The most common infection type was bronchopneumonia (72.5%), followed by bloodstream infections (42.75%), skin infections (20%), gastroenteritis (15%), urinary tract infections (7.5%), and mucositis (5%). This is similar to a study a previous study, which revealed that a significant association between infection type, especially non-upper respiratory tract infections, and the incidence of co-infection in children with febrile neutropenia associated with chemotherapy.[16] Inaba *et al.*[14] reported that among 2,420 cases of infection-related complications, 1,107 cases were diagnosed with febrile neutropenia and 1,313 cases were clinically or microbiologically diagnosed infections. The most common infections found were upper respiratory tract infections in 389 cases, followed by ear, bloodstream, and gastrointestinal tract. Infections occurred more frequently during the intensive management phase, such as remission induction and re-induction. However, respiratory tract and ear infections, presumably of viral origin, also occurred during the continuation phase. Compared with standard-risk ALL patients, high-risk ALL patients received more intensive management and had a higher incidence of febrile neutropenia ($P<0.001$) and infection ($P=0.043$).[17] Poor neutrophil surge after dexamethasone administration (reflecting poor bone marrow reserves) was also associated with a higher chance of developing infections ($P<0.001$).[17]

The administration of prophylactic antibiotics did not have a significant association with sepsis in our subjects. This result differed from a Toronto study, which found that in ALL patients who received intensive chemotherapy, the use of prophylactic levofloxacin led to a significant decrease in bacteremia.[18] This difference might have been due to the small number of patients who were given prophylactic antibiotics in our study (12.21%).

The phase of chemotherapy also had no significant association with sepsis. The highest incidence of sepsis was found in the induction phase (50% of subjects). The incidence and pattern of septicemia in our study is in agreement with those in a previous study concluding that septicemia was mostly found during induction phase chemotherapy for ALL.[4] A study found 66.8% and 56.1% of patients were originally classified as having a low and high risk of

septicemia, respectively.[4] Even though no significant association was found, the phase of chemotherapy may indirectly contribute to sepsis. In the induction phase, patients are at the highest risk of infection due to the underlying active leukemia and intensive chemotherapy. They also undergo several invasive procedures, such as intravenous line insertion, bone marrow aspiration, and lumbar puncture. Another peak period of sepsis is in the re-induction phase at 32-34 weeks, where high doses of dexamethasone and cytarabine are given for a longer period, which can cause more severe mucosal damage and secondary infection. Prophylactic antibiotics and close monitoring in the hospital may reduce the incidence of sepsis during this period.[4]

A limitation of our study was its retrospective design, which carries the potential for selection bias. Selection bias may occur due to the prior knowledge of the author in identifying the samples with the known and wanted outcome. As it was done in a single center, the external validity of the study may be limited. We recommend future studies to use a prospective cohort design. We conclude that older age and the presence of co-infection are significantly associated with sepsis in children with ALL and febrile neutropenia.

Conflict of interest

None declared.

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