Sepsis in Children with Acute Lymphoblastic Leukemia

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ABSTRACT

Background: Sepsis is the leading cause of morbidity and mortality in children worldwide, with around 75,000 inpatients each year and nearly 50% dying in pediatric hospitals. Acute lymphoblastic leukemia (ALL) in childhood is a malignancy originating from lymphoid progenitor cells, usually at the age of 2–6 years. Children with ALL contribute 30% to childhood cancer cases under 15 years old. Sepsis in pediatric patients increases mortality significantly. A previous study showed that the prevalence of sepsis in pediatrics is still high. Thus, this study aims to report ALL patients with sepsis in our institution.

Methods: This study was a descriptive cross-sectional study at the National Cancer Center (NCC) - Dharmais Cancer Hospital. We recruited acute lymphoblastic leukemia (ALL) patients aged 2-18 years with suspected or documented sepsis based on Systemic Inflammatory Response Syndrome (SIRS) by The International Consensus Conference on Pediatric Sepsis. The data were collected by medical records from January 2014 to December 2018.

Results: A total of 94 pediatric patients in the study included 57 males and 37 females with an average age of 5 years. The age range was 1–18 years with a median age of 5 years. The prevalence of sepsis in pediatric with ALL was 11 patients (11.7%) and 45.5% of deaths. The clinical conditions were as follows: abnormal temperature (8 [72.7%]), abnormal blood pressure, systolic (7 [63.6%]) and diastolic (7 [63.6%]), abnormal pulse rate (9 [81.8%]), abnormal respiratory rate (8 [72.7%]), and normal saturation (6 [54.5%]). We also did a laboratory check followed by all sepsis patients who had abnormal leukocytes (11 [100%]), and abnormal lymphocytes count (8 [72.7%]).

Conclusions: The mortality rate and prevalence of sepsis in children with ALL in our institution are still high. Further prospective studies are required to explore the risk factors and predictors of sepsis based on its severity and adherence of health workers to implement guidelines on patients with sepsis in the hospital.

INTRODUCTION

Sepsis is the leading cause of morbidity and mortality in children worldwide, with around 75,000 inpatients each year and nearly 50% dying in pediatric hospitals [1]. Currently, sepsis is defined as multi-organ dysfunction resulting from an unregulated host response to infection, which affects the course of the disease and the prognosis in the patient. It is a potentially life-threatening inflammatory response of the body, which increases morbidity and mortality significantly [2–4]. However, sepsis is caused by an immune response triggered by a bacterial, fungal, parasitic, or viral infection. The infection comes from within the hospital (nosocomial) or the environment (acquired from the community) [5].

The global burden of sepsis, however, is difficult to determine. It is characterized by a generalized pro-inflammatory, which can lead to widespread tissue injury. It encompasses a clinical spectrum of severity, including severe sepsis, septic shock, and multi-organ failure, especially in cancer patients. It implies that the mortality in sepsis varies according to patient characteristics as well [6].

According to GLOBOCAN 2018, there were 437,033 new cases of leukemia with a mortality rate of 309,006 cases [7]. Acute lymphoblastic leukemia (ALL) is a malignancy generated from lymphoid progenitor cells, which can affect adults and children who reach the age of 2–18 years [8]. The children with an underlying diagnosis of malignancy were at high risk for developing serious infections. Chemotherapy and radiation therapy regimens used to treat underlying cancer often cause prolonged marrow aplasia. Through the use of aggressive treatment protocols combining chemotherapy, radiation,

and surgery, the prognosis for patients with childhood malignancies has substantially improved [9]. Within the spectrum of sepsis syndrome, severe sepsis refers to children with shock or other organ dysfunction as a high-risk group targeted for intervention studies in pediatric intensive care units (PICU) [10]. Limited access and complications of initial therapy cause significant morbidity and mortality [11].

Based on global data of sepsis in children, it is estimated that infection causes the majority of deaths (nearly 60%) in children under five years of age. According to the data of Surviving Sepsis Campaign 2012, the mortality rate of sepsis is about 41% in Europe versus 28.3% in the United States [12]. A multicenter study in Australia and New Zealand that included 101,064 critical patients showed that the mortality rate in sepsis has decreased over the years from around 35%. [13]. Abdelmabood et al. [14] showed that sepsis in children with acute lymphoblastic leukemia in developing countries was 15%. In Indonesia, sepsis in malignancy was 11.1% with an overall mortality rate of 88.2% and the survival rate of 44.4% [14–16]. Based on the previous study, the prevalence of sepsis was low, but the mortality was high. Therefore, this study aims to report ALL patients with sepsis in our institution.

METHODS

This descriptive cross-sectional study was conducted at the National Cancer Center (NCC) - Dharmais Cancer Hospital. Dharmais Cancer Hospital is a tertiary care unit in Indonesia with 27 beds in the general inpatients unit and 2 beds in the Pediatric Intensive Care Unit (PICU). The data were taken from January 2014 until December 2018.

We recruited acute lymphoblastic leukemia (ALL) patients aged 0–18 years with suspected or documented sepsis based on Systemic Inflammatory Response Syndrome (SIRS) by The International Consensus Conference on Pediatric Sepsis [5,17]. The patients not fulfilling the eligibility criteria were those aged > 18, and those unwilling to provide consent were excluded from the study. This study comprised 94 pediatric patients with ALL.

Systemic inflammatory response syndrome (SIRS) is defined by the presence of ≥ 2 of the following criteria (temperature or abnormal white blood cell count must meet one of the criteria): (1) abnormal temperature (< 36°C or > 38.5°C), (2) abnormal pulse rate (children aged 1–5 years: normal range of systolic is 95–110 mmHg and diastolic 56-70 mmHg; children aged 6–13 years: normal systolic is 97–112 mmHg and diastolic 57–71 mmHg; children aged 13–18 years: normal range of systolic is 112–128 mmHg and diastolic 66–80 mmHg.), (3) Increased respiratory rate Children aged 1–2 years:

20–30; 3–5 years: 20–25; 6-11 years: 14–22; 12–15 years: 12–18; 16–18 years: 16–20, or use of mechanical ventilation in acute pulmonary disease), (4) abnormal white blood cell count (according to age) (normal for children under 2 years: 6,200 to 17,000 mcL; children over 2 years: 5,000 to 10,000 mcL) and abnormal lymphocyte (normal: 20 to 40 percent), (5) Laboratory result of C-Reactive Protein (CRP) (negative: < 1 mg/dl), and Procalcitonin (PCT) (negative: PCT < 0.5 mg/dl). Besides, we checked the laboratory test and mortality.

The statistics were assessed by SPSS Version 25. Categorical variables were described using frequencies. Continuous variables were described by the median, interquartile range, minimum, and maximum values. The ethical review was approved by the Dharmais Cancer Hospital ethics committee.

RESULTS

Demography

A total of 94 pediatric patients in the study included 57 males and 37 females. The age range was 1–18 years with a median age of 5 years. The prevalence of sepsis in pediatric patients with ALL was 11 patients (11.7%). Most of the stratifications of ALL were high risk (79.8%) and in maintenance chemotherapy phases (64.9%) (**Table 1**).

Table 1. Baseline characteristics of the patients with ALL

Variables	n (%)
Age (median, min - max)	5, 1–8 years
Sex	
Male	57 (60.6)
Female	37 (39.4)
Sepsis	
Yes	11 (11.7)
No	83 (88.3)
Stratification Risk	
Standard Risk	19 (20.2)
High Risk	75 (79.8)
Chemotherapy Phase	
Induction	19 (20.2)
Consolidation	10 (10.6)
Reinduction	4 (4.3)
Maintenance	61 (64.9)

Clinical and Clinicopathological Condition

The clinical condition of ALL patients with sepsis was assessed based on the patient's vital signs as follow: abnormal temperature (8 [72.7%]), abnormal blood pressure that systole (7 [63.6%]), abnormal diastole (7 (63.6%)), abnormal pulse rate (9 [81.8%]), abnormal

respiratory rate (8 [72.7%]), and normal saturation (6 [54.5%]). We also did a laboratory check followed by all sepsis patients who had abnormal leukocytes (11 [100%]) and Lymphocytes (8 [72.7%]) (**Table 2**).

Table 2. Clinical condition and clinicopathological sepsis in pediatric with ALL

Variables	n (%)
Temperature	
Normal	3 (27.3)
Abnormal	8 (72.7)
Blood pressure	
Systole	
Normal	4 (36.4)
Abnormal	7 (63.6)
Diastole	
Normal	4 (36.4)
Abnormal	7 (63.6)
Pulse rate	
Normal	2 (18.2)
Abnormal	9 (81.8)
Respiratory rate	
Normal	3 (27.3)
Abnormal	8 (72.7)
Saturation	
Normal	6 (54.5)
Abnormal	5 (45.5)
Leukocytes	
Normal	0 (0.0)
Abnormal	11 (100.0)
Lymphocytes	
Normal	3 (27.3)
Abnormal	8 (72.7)
Neutrophil Lymphocytes Rate (NLR)*	1.4 ± 4.8
Hemoglobin*	8.2 ± 2.1
Blood urea*	25.0 ± 27.8
Creatinine*	0.4 ± 0.3
PH levels*	7.3 ± 0.2
PO2*	133.9 ± 98.9
PCO2*	38.1 ± 10.6
C-Reactive Protein (CRP)	
Normal	0 (0.0)
Abnormal	11 (100.0)
Procalcitonin (PCT)	
Normal	1 (9.1)
Abnormal	10 (90.9)
Culture	
No	2 (18.2)
Blood	6 (54.5)
Urine	2 (18.2)
Sputum	1 (9.1)
Microbiology	
Pseudomonas sp.	2 (18.2)
Pseudomonas putida	3 (27.3)
Staphylococcus aureuginosa	3 (27.3)
Streptococcus pneumoniae	1 (9.1)

*Data were presented as median ± interquartile

Table 3. Disposition of sepsis patients

Variables	n (%)
Admission	
PICU	5 (45.5)
General inpatients unit	6 (54.5)
LOS (days) (median ± IQR)	17 ± 9
Mortality rate	7 (63.6)
Discharge home	6 (54.5)

Disposition of Sepsis Patients

Dharmais Cancer Hospital has twenty-seven beds in the general inpatients unit and two beds in PICU. Disposition of sepsis patients is as follow: admission PICU (5 [45.5%]), general inpatients unit (6 [54.5%]), and discharged (6 [54.5%]). The median of Length of Stay (LOS) patient sepsis was 17 days with a mortality rate of 45.5% (**Table 3**).

DISCUSSION

Sepsis has been defined as a life-threatening condition caused by a host response to infection. This study reported the prevalence of sepsis in pediatric patients with ALL of 11.7% and 45.5% of deaths. In Southwest China, a multicenter prospective study of severe pediatric sepsis showed that the prevalence of sepsis in four provinces (Chongqing, Sichuan, Guizhou, and Yunnan) was higher than in Indonesia (17.9%, 16.2%, 22.4%, and 18.0%, respectively) [18]. An observational study in India about predictors of outcome and progression of pediatric sepsis reported that 13% progressed to severe sepsis, but in Philadelphia was 8.9% [1,19]. According to the data of Surviving Sepsis Campaign 2012, the mortality rate of sepsis is about 41% in Europe versus 28.3% in the United States [12]. Another study showed that sepsis in children with acute lymphoblastic leukemia in developing countries was 15% [14].

There was no significant difference in the sex and age distribution of the patients compared with those of other reports [18,20]. This finding was also reported by Sano et al. [21]. Our study has shown greater sepsis among males as compared to females. Male and female patients demonstrate different sex steroid hormone responses to infection [22]. Research by Nasir et al. [23] showed that mortality in males was higher than in females with sepsis in adults. This phenomenon had been observed in animal studies where females had been known to have a survival advantage in terms of both immunologic as well as cardiovascular responses. However, most clinical studies have failed to show consistent differences in sepsis outcomes to gender [24,25].

Sepsis is an important cause of morbidity and mortality in children. Therefore, it is important to identify sepsis at an early stage to prevent its progression. The prevalence of sepsis, the level of severity, and mortality in developing countries are higher than in developed countries because of child nutrition, quality of health services, and health workers. The predictors of mortality included positive blood cultures, multiorgan dysfunction, late hospital admissions, severe acute malnutrition, and the requirement of supportive care [9,13,19]. The predictors of progression to septic shock were abnormal leukocyte count, neutrophil, temperature, culture positivity, severe acute malnutrition, CRP, and PCT [5,6,19,26,27].

Sepsis caused by infection remains a major cause of mortality and morbidity among children. Blood culture though the gold standard requires a lot of time for diagnosis; hence, it is necessary to rely on early diagnostic markers such as blood counts, CRP, and PCT [26]. CRP and PCT were the inflammatory markers for patients with clinically suspected sepsis. In this study, the laboratory results show abnormal CRP (100%) and PCT (90.9%) in ALL pediatric patients with sepsis. CRP, one of the biomarkers that have been in longer use in pediatric sepsis [28], is a non-specific, acute-phase protein that increases 4-6 hours after exposure to an inflammatory trigger (infectious or not) and has an 8-hour doubling time, peaking from 36 to 50 hours after the trigger stimulus. CRP has a 19-hour half-life. Its levels decrease rapidly with the resolution of inflammation and are usually high in invasive bacterial infections [29].

Elevation of PCT levels usually occurs earlier during infection than the elevation of CRP levels, peaking at approximately 24–36 hours. A study of critically ill pediatric patients showed that the accuracy of PCT measurement in detecting bacterial infections is better than that of other markers, especially CRP [30]. At our institution, PCT and CRP biomarkers are used when the patient's hemodynamics are abnormal. Despite advances in diagnosis and treatment, bacterial sepsis remains a major cause of pediatric morbidity and mortality, particularly among neonates, the critically ill, and the growing immunocompromised patient, especially cancer [31].

Blood cultures are essential for the diagnosis and further appropriate treatment in children with suspected sepsis [32]. In our hospital, not all pediatric patients have their blood cultures checked because of a lack of adherence to the guidelines in implementing the blood culture test. Children with suspected sepsis will be treated empirically or closely monitored for at least 3 days awaiting blood culture results and given after antibiotics.

There is enough evidence to support the recommendation of drawing blood culture in immunocompromised patients (like cancer patients) with a temperature of 380C or higher, or even with a sustained low-grade fever [33,34]. The real challenge arises if the isolated microorganism is part of the normal flora of the patient, for example, coagulase-negative *Staphylococci*, viridian's group *Streptococci*, *Corynebacterium* sp., *Propionibacterium acnes*, *Bacillus* sp., and some *Clostridium* sp. [33,34]. The presence of only one positive blood culture in two or more serial draws performed in a short period would be more suggestive of contamination [31]. In any event, there is no definitive method to differentiate contamination and true bacteremia, and in each case, the interpretation of the results of blood culture will ultimately rest with the clinician [34].

Early detection of septic shock is critical to establish an optimal, time-sensitive treatment. Thus, it is necessary to have clinical criteria adequate to current definitions. Weiss et al. observed a moderate adherence to the consensus definitions in a study carried out in 26 countries [10]. The development of signs and symptoms that are not sufficiently clear should be considered in the first examination for early detection. The simplification of diagnostic criteria allows prompt identification and better survival of patients with septic shock [35-38]. Some studies have pointed out that patients outside the intensive care unit (ICU) experienced delays in early detection and, therefore, in their treatment and referral to the ICU [39-41]. However, in this study, 54.5% of patients were treated in general inpatients units due to limited PICU.

Having said that, this result must be looked at while considering the limitations of this study, such as not analysis of risk factors for incidence sepsis and limited sample size. Besides, the small number of cases can be probably due to the diagnosis of sepsis that was not recorded in the medical records, leading to information bias.

CONCLUSIONS

In conclusion, the mortality rate and prevalence of sepsis in children with ALL in our institution are still high. Further prospective studies are required to explore the risk factors and predictors of sepsis based on its severity in pediatric patients with ALL. On the other hand, research about the adherence of health workers to implement guidelines on patients with sepsis in the hospital is strongly recommended.

DECLARATIONS

Competing of Interest

The authors declare no potential conflicts of interest.

Acknowledgment

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