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Incidence of Candidemia in Neutropenia with Administration of Broad-Spectrum Antibiotics in Pediatric Patients with Acute Lymphoblastic Leukemia

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Abstract

Candidemia is one of the main causes of morbidity and mortality in patients with hematological malignancies. However, the difficulty in establishing a definitive diagnosis causes these high rates. Therefore, a rapid diagnosis process is needed for the early stages of infection as the initial clinical management in pediatric patients with malignancy, especially accompanied by neutropenia. This study aims to determine the risk factors for candidemia in children using PCR (Polymerase Chain Reaction). A cross-sectional study design was used to determine the relationship between neutropenia and broad-spectrum antibiotics with the incidence of candidemia in pediatric patients with acute lymphoblastic leukemia (ALL). The results were analyzed statistically. 33 pediatric patients who met the inclusion criteria, 22 (66.67%) were positive for candida. The sample was dominated by male (66.67%) with a mean age of 4.5 years and had undergone the standard (14 patients) and high-risk (19 patients) chemotherapy protocols. The correlation test revealed no significant correlation between the administration of broad-spectrum antibiotics and the incidence of candidemia in pediatric patients with ALL (p= 0.052), neutropenia recorded a notable relationship to those patients (p=0.033). This study shows that neutropenia is a risk factor that affects the prevalence of candidemia in pediatric patients with ALL. Children with ALL who have severe neutropenia are at an increased risk of developing candidemia.

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INTRODUCTION

Candidemia is a leading cause of morbidity and mortality among patients with hematologic malignancies, and its incidence has been on the rise in recent years.[1] In the United States, the occurrence of candidemia in children varies from 0.35 to 0.81 cases per 1000 hospitalized patients. Among hospitalized children with hematological malignancies, 1.25 episodes per 1000 cases were reported, with *Candida albicans* being the most common cause.[2] Kalista et al. reported that the prevalence of candidemia in pediatric patients with hematological malignancies and solid tumors at RSCM was 8.7% and 23.1%, respectively.[3] The mortality rate associated with candidemia is as high as 60% in children with hematological malignancies.

Pediatric patients with blood malignancies often undergo extended treatment courses, particularly chemotherapy. Prolonged exposure to high chemotherapy doses can lead to neutropenia in pediatric patients, and the use of broad-spectrum antibiotics can increase the incidence of infections, particularly those caused by *Candida* spp..[1]

The mortality rate due to candidemia was significantly higher in patients with neutropenia, exceeding that in non-neutropenic patients by 13.6%.[5] Challenges in establishing a definitive diagnosis contribute to these elevated rates. Consequently, a prompt diagnosis in the early stages of infection is crucial for initial clinical management in patients with neutropenia. One method to achieve this is Polymerase Chain Reaction (PCR) for pediatric patients suspected of having candidemia, as it demonstrates reasonably high sensitivity compared to the culture method.[6]

MATERIALS AND METHODS

Research Subject

The population in this study were hospitalized pediatric patients with acute lymphoblastic leukemia and neutropenia who were undergoing chemotherapy and had received broad-spectrum antibiotics. A total of 29 pediatric patients with acute lymphoblastic leukemia who met the inclusion and exclusion criteria were selected as samples based on the Receiver Operating Characteristic (ROC) diagnostic test formula.

Methods

Research design

This study is a preliminary study. This study used a cross-sectional design to determine the relationship between neutropenia and broad-spectrum antibiotics with the incidence of candidemia in pediatric patients with acute lymphoblastic leukemia (ALL). Samples were taken by consecutive sampling from patients who were suspected of candidemia in February - May 2022 at the pediatric ward (IRNA IV) of Dr. Saiful Anwar Hospital, Malang.

Inclusion Criteria

The inclusion criteria in this study were patients with ALL who experienced neutropenia, had received broad-spectrum antibiotic therapy for at least 5 days, and were not taking antifungal drugs (at least 1 month before the study). The degree of neutropenia used to classify each case was as follows: mild neutropenia (absolute neutrophil count (ANC) of 1000-1500 cells/mm^3), moderate neutropenia (ANC of 500-999 cells/mm^3) and severe neutropenia (ANC od <500 cells/mm^3).

Exclusion Criteria

Exclusion criteria in this study were pediatric patients with malignancies other than ALL and immunodeficiency conditions due to other causes.

Research procedure

Blood samples (5 ml) were drawn twice, namely when the patient came to determine the degree of neutropenia and during a conventional PCR examination. Blood samples were centrifuged at 3000 rpm for 10 minutes, and the serum was stored at 4 °C for a follow-up examination. PCR assay with the serum, performed at the start of the study, used 1 pair of

primers to amplify the target genome sequence.

Data Analysis

The data in this study were not normally distributed, so the follow-up test used was the Mann-Whitney, Kruskal-Wallis, Fisher, and Chi Square tests with = 0.05 and Confidence Interval (CI) of 95%, run by SPSS for Windows 25 software. The relationship between neutropenia with the incidence of candidemia in pediatric patients with ALL was measured using the Fisher correlation test, while administration of broad-spectrum antibiotics was measured using Chi Square.

RESULTS AND DISCUSSION

Results

Three pediatric patients who met the inclusion criteria (Table 1), 22 (66.67%) were positive for candida. The sample was dominated by male (66.67%) with a mean age of 4.5 years and had undergone the standard (14 patients) and high-risk (19 patients) chemotherapy protocols. The majority of patients had good nutritional status (22 patients), followed by malnourished (5 patients), undernourished (3 patients), overweight (1 patient), and obese (2 subjects). As many as 18 patients were still in the induction phase of chemotherapy, 7 in the consolidation phase, 2 in the intensification phase, and 4 in the maintenance phase. During the chemotherapy, 5 patients experienced moderate neutropenia (4 patients with negative candida and 1 patient with positive candida in PCR), and 28 patients have severe neutropenia (7 patients with negative candida and 21 patients with positive candida in PCR). Ceftriaxone was administrated to 24 patients with severe neutropenia; Cotrimoxazole for 5 patients with moderate neutropenia; Cloxacillin with gentamycin for 1 patient with positive candida in PCR; Meropenem for 2 patients with positive candida in PCR; Cefoperazone for 1 patient with positive candida in PCR. A total of 6 patients with positive candida in PCR experienced febrile neutropenia.

No patient was recorded to have very severe neutropenia (ANC od <500 cells/mm^3). In contrast to patients with severe neutropenia, patients with moderate neutropenia (ANC of 500-999 cells/mm^3) typically have negative candida findings. This study showed a significant relationship (p value of 0.033, in which a p value of < 0.05 is considered significant) between neutropenia and candida results on PCR, whereas the correlation test unveiled no notable correlation (p value of 1.000) between antibiotic therapy and candidemia.

Discussion

Mortality rate of 35–38%, fungal infections are a significant cause of morbidity and mortality in patients treated for hematological malignancies.[7] Wang et al. reported 123 episodes of children with fungal infections in Queensland, Melbourne, Perth, and Sydney pediatric hospitals, of which 119 were pediatric patients with ALL.[8]

Cases of candidemia continue to increase along with the increasing number of patients with impaired immunity and the use of invasive devices. In patients with malignancy, decreased immunity and damage to the gastrointestinal mucosal barrier are risk factors for developing candidiasis, including candidemia. Candidemia was defined as the presence of Candida spp. in blood.[9,10] Marwa et al. found the incidence of candidemia in pediatric patients with acute lymphoblastic leukemia in Egypt reached 75%.[11]

Table 1. Patient Characteristics

Characteristics	Negative Candida	Positive Candida	p
Sex, f(%)			
Male	8 (36.4)	14 (63.6)	0.709
Female	3 (27.3)	8 (72.7)	
Age (years), median (min-max)	5 (2-13)	4.5 (1.5 – 15)	0.908
Nutritional Status, f (%)			
Malnourished	3 (60)	2 (40)	0.307
Undernourished	1 (33.3)	2 (66.7)	
Well-nourished	6 (27.3)	16 (72.7)	
Overweight	1 (100)	0 (0)	
Obese	0 (0)	2 (100)	
Diagnosis			
ALL-L2	8 (32)	17 (68)	1.000
ALL-L2 (relapse)	3 (37.5)	5 (62.5%)	
Antibiotic Therapy			
Ceftriaxone	6 (25)	18 (75%)	0.103
Cloxacillin + gentamisin	0 (0)	1 (100%)	
Cotrimoxazole	4 (80)	1 (20%)	
Meropenem	0 (0)	2 (100%)	
Cefoperazone	1 (100)	0 (0%)	
	0 (0)	1 (100%)	
Chemotherapy Type			
Standard	5 (35.7)	9 (64.3%)	1.000
High-risk	6 (31.6)	13 (68.4%)	
Chemotherapy Phase			
Induction	8 (44.4)	10 (55.6%)	0.339
Consolidation	1 (14.3)	6 (85.7%)	
Intensification	0 (0)	2 (100%)	
Maintenance	2 (50)	2 (50%)	
ANC Total, median (min-max)	420 (70-950)	350 (10-790)	0.302
Neutropenia duration (days), median (min-max)	7 (4-14)	6 (3-21)	0.861
Febrile Neutropenia, f (%)	2 (25)	6 (75)	0.687

This study found that severe neutropenia was associated with the incidence of candidemia in pediatric patients with ALL. This is in line with the findings of previous studies, which stated that the risk factors for candidemia in children with acute lymphoblastic disease included severe neutropenia (neutrophil count <500/ul) for more than 10 days along with the presence of a bacterial infection that is resistant to previous broad-spectrum antibiotics.[12] The prolonged duration of neutropenia is associated with a longer period of chemotherapy, leading to a higher risk for candidaemia.[13]

Gastrointestinal bacterial colonization is often affected during treatment with chemotherapy,[14] either due to damage to the mucosal barrier or the use of broad-spectrum antibiotics and other antimicrobials. The use of beta-lactam and cephalosporins antibiotics in leukemia patients can increase the risk of MDRO, including broad-spectrum beta-lactamase resistance (ESBL).[15]

Polymerase Chain Reaction (PCR)

Non-culture-based methods, such as DNA detection by PCR, have been developed to aid in the rapid diagnosis of candidemia, enabling faster initiate empiric antifungal therapy and reducing mortality in pediatric patients with acute leukemia.[20,21] El-Ashry and Ragab[18] reported that the RT-PCR test has a sensitivity level of 100% compared to the results of blood cultures. This is supported by Gupta et al. [19] that stated the sensitivity, specificity, and positive and negative predictive values of RT PCR were 82.7%, 54%, 72.9%, and 67.5%, respectively. Furthermore, Ratridewi et al. noted that the sensitivity and specificity of PCR reached 69.2% and 71% in diagnosing systemic candidiasis in children with malignancy with severe neutropenia, respectively

(Figure 1). However, a need to further assess other potential risk factors in the incidence of candidemia in malignancy cases have to be considered clinically.[22, 23,24,25]

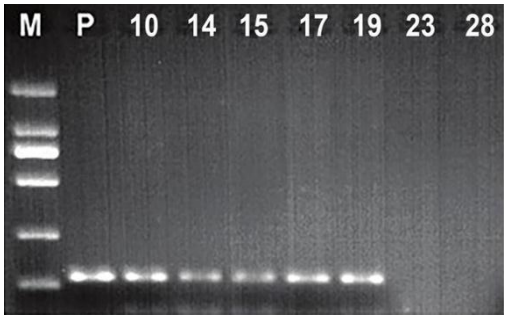

Figure 1. PCR results for candida in pediatric patients with Acute Lymphoblastic Leukemia (ALL) at Dr. Saiful Anwar Hospital, Malang. Marker gene URA 3, ARG 4, HIS 1, LEU 2, SAT1 was used.

STRENGTH AND LIMITATION

The current research was limited by its study design, short time-period and low sample size in a single center. Further large-scale research with long-term follow up is needed to evaluate the contribution of risk factors and the other preexisting medical conditions in ALL children with candidemia.

CONCLUSIONS

Candidemia is one of the leading causes of morbidity and mortality in patients with hematologic malignancies, with an increasing incidence over the last few decades. The risk factors for candidemia in pediatric patients with acute leukemia are prolonged neutropenia along with the presence of resistant bacterial infections. The main problem that leads to a high mortality rate is difficulties in establishing a definitive diagnosis. Thus, PCR examination can be used as an effective and efficient diagnostic tool for candidemia with high sensitivity and specificity values.

FUNDING

This study did not receive funding

ETHICAL CLEARANCE

This study was approved by the Research Ethics Committee of Saiful Anwar General Hospital Malang (Reference letter number 400/085/K.3/10.7/2022).

CONFLICT OF INTEREST

There was no conflict of interest in this study.

AUTHOR CONTRIBUTION

IR is the main author and contributed the most in writing the study. CC oversaw data collection and contributed in writing the manuscript. SLW oversaw data analysis and contributed in writing the manuscript. SN contributed in enriching the discussion and overall writing of the manuscript.

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