Berkala Ilmu Kedokteran
Vol. 41, No. 4, Desember 2009: 178-182

The risk factor of urinary tract infection in patient with leukemia

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ABSTRACT

Melati Dini Hari, Soetaryo, Pungky Ardani Kusuma - ***The risk factor of urinary tract infection in patient with leukemia***

Background: Urinary tract infection (UTI) is one of most common infectious diseases in patients wuth leukemia. Some researchers showed that the prevalence of UTI was the third highest after pneumonia and gastrointestinal tract infection among children with leukemia. UTI may be affected by many factors, i.e. host, microorganism, and environment. *E. coli*, Klebsiella, dan Proteus are the most common bacterial etiology of UTI in leukemia.
Objective: The aim of this research was to know the risk factor of UTI in children with leukemia.
Method: This research used case-control design. Subjects of this study were children (0-15 years old) with leukemia who came to Department of Pediatrics, Dr. Sardjito Hospital since January 1st, 2000 until October 3rd, 2008. There were 38 patients in case group and 109 patients in the control group. Data collected from medical records were age, gender, nutritional status, type of leukemia, treatment phase of leukemia, and absolute neutrophil count. Risk factors analyzed were age, gender, nutritional status, and neutropenia. UTI was diagnosed by bacterial culture and bacterial count.
Result: Univariate analysis showed that female gender was the risk factor of UTI (OR 2.35; CI 1.10-5.00), meanwhile age less than 5 years old (OR 0.48; CI 0.22-1.06), poor-fair nutritional status (OR 1.20; CI 0.52-2.78), and neutropenia (OR 0.73; CI 0.35-1.55) were not risk factors of UTI. Multivariate analysis showed that female gender was the risk factor of UTI (OR 2.36; CI 1.08-5.14).
Conclusion: Female gender was a risk factor of UTI in children with leukemia

Keywords: leukemia – children – gender - urinary tract infection - risk factors

ABSTRAK

Melati Dini Hari, Soetaryo, Pungky Ardani Kusuma - ***Faktor risiko infeksi saluran kemih pada pasien leukemia***

Latar Belakang: Infeksi saluran kemih (ISK) merupakan salah satu infeksi yang sering terjadi pada pasien leukemia. Dalam beberapa penelitian, kejadian ISK menempati urutan ketiga setelah pneumonia dan infeksi saluran pencernaan sebagai infeksi terbanyak yang ditemukan pada anak dengan leukemia. ISK dapat dipengaruhi oleh berbagai macam faktor, yaitu faktor inang, faktor kuman, dan faktor lingkungan. *E. coli*, Klebsiella, dan Proteus merupakan bakteri terbanyak penyebab ISK pada leukemia.
Tujuan: Penelitian ini bertujuan untuk mengetahui faktor risiko infeksi saluran kemih pada anak dengan leukemia.
Metode: Desain penelitian adalah kasus-kontrol. Subyek penelitian adalah pasien leukemia berusia 0-15 tahun, yang datang ke SMF Anak RS. Dr. Sardjito sejak 1 Januari 2000 sampai 31 Oktober 2008. Didapatkan sebanyak 38 orang pada kelompok kasus dan 109 orang pada kelompok kontrol. Data diambil dari rekam medis dan dicatat usia, jenis kelamin, status gizi, jenis leukemia, fase pengobatan leukemia dan jumlah neutrofil absolut. Faktor risiko yang dinilai adalah usia, jenis kelamin, status gizi dan neutropenia. Diagnosis ISK dibuktikan dengan kultur dan angka kuman.
Hasil: Hasil analisis univariat menunjukkan bahwa jenis kelamin perempuan adalah faktor risiko ISK (OR 2,35; KI 1,10-5,00), sementara usia < 5 tahun (OR 0,48; IK 0,22-1,06), status gizi buruk-kurang (OR 1,20; IK 0,52-2,78) dan neutropenia (OR 0,73; IK 0,35- 1,55) bukan merupakan faktor risiko. Hasil analisis multivariat menunjukkan bahwa jenis kelamin perempuan merupakan faktor risiko ISK (OR 2,36; IK 1,08-5,14).
Simpulan: Jenis kelamin perempuan merupakan faktor risiko ISK pada leukemia.

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INTRODUCTION

Leukemia is the most common malignancy in children. Acute childhood leukemia constitutes 30-40% of malignancies, and 97% of all leukemia. Two types of acute leukemia are acute lymphoblastic leukemia (ALL) (82%) and acute myeloblastic leukemia (AML) (18%).[1] In US it was reported that there were 3250 children who were diagnosed to have leukemia every year. In Japan, Singapore, and Phlippines the incidence of leukemia per year in children under 14 year old is around 35-49/1 000 000 children.[2]

Since 1960, the cure rate of ALL has been improved from about 30% to 5-year survival rate of around 80-86%.[3] AML has worse prognosis compared to ALL.[1] Survival rate of AML is around 41%.

Around 34% mortality of malignancy in children is caused by leukemia. Mortality rate of leukemia is 30-40%.[4] Around 70% mortality in leukemia is caused by infection.[5] Life-threatening infection usually occurs in induction phase, while death in the first two weeks is usually caused by bleeding and leukostasis.[6] Infection in malignancy is the result of interaction of immunocompromized condition caused by malignancy and chemo-therapeutic effect, and organ dysfunction as well.[7] Lower respiratory tract infection is the most important infection commonly found in leukemia patients.[8-10] Chua found that the most common infections in childhood leukemia were infections of respiratory tract (38.9%), gastrointestinal tract (8.9%), urinary tract (7.8%), skin and soft tissue (5.5%), and ear (2.2%).[8] Dubey *et al.* found that from 43 fever episodes in children malignancy, 36% had been proven microbiologically.[9] Pneumonia was the commonest infection (26%), while UTI was found in 1 patient (7%). In a study on children with malignancy in Turkey out of 425 infections, the most prevalent was lower respiratory tract infection (32.7%), followed by UTI (32.7%), and mouth and upper respiratory tract infection (15.9%).[10] Auletta *et al.* found three most common infections in children with hematologic malignancy and solid tumor[11] were otitis media, septicemia and UTI. There were 8.1% leukemia patients who had UTI.[12] UTI in leukemia patients was also studied by others.[7,13]

The occurrence of infection in leukemia is often associated with low neutrophil count as the effect of leukemia treatment. Neutropenia is found in 74.1% infection episodes.[14] Several researchers investigated the relationship between absolute neutrophil count and infection occurrence in leukemia. Risk of bacterial infection increased in patients who have absolute granulocyte count less than 500/mm^3, and particularly less than 200/mm^3.[15] Leukemia patient who had absolute neutrophil count less than 500/mm^3 had higher risk to have infection and had a high mortality rate.[8] The higher absolute neutrophil count the shorter the fever duration, $r = -0.21$ ($p > 0.05$).[9] Akova *et al.* found that patients with granulocyte count < 100/mm^3 had higher risk of infection compared to those with granulocyte count >100/mm^3, OR: 2.72 95%CI 1.72-4.28, $p<0.001$.[16] Meanwhile, Auletta *et al.* found that patients with absolute neutrophil count more than 500/mm^3 had higher risk of infection.[11]

Until recently, there was no study on neutropenia as one of the risk factors of UTI in children with leukemia in Dr. Sardjito Hospital. By understanding the relationship of neutropenia, gender, age, and nutritional status as risk factors for UTI infection in children, UTI occurrence can be prevented, particularly in immunocompromized children with leukemia. Therefore, infection as one of the most common causes of mortality in leukemia can be decreased.

METHOD

It was a case-control study involving patients with leukemia. Risk factors of UTI investigated were neutropenia, gender, nutritional status, and age. Achievable population was children with leukemia who came to Dr. Sardjito Hospital between January 1st, 2000 and October 31st, 2008. Inclusion criteria were leukemia patients under 15 years old who were hospitalized or visiting Outpatient Clinic of Pediatric Department, Dr. Sardjito Hospital. Patients with history of anatomical and functional abnormality of urinary tract, phimosis, constipation, and whose medical records were not complete were excluded from this study.

Sample size of this study was determined based on assumption that neutropenia was the risk factor

of UTI, with odds ratio of 0.7, significance level of 0.05, and statistical power of 80%. Minimum sample size for this group was 69 patients. The ratio of case and control groups was 1:3. In this study, there were 46 cases and 138 controls.

The difference in proportion of the two groups was analyzed with chi-square. Multivariate analysis with logistic regression was used to obtain the best and simplest model that illustrated the relationship between independent and dependent variables. The clinical significance level was stated in 95% confidence interval.

RESULTS

From medical records of children with leukemia who came to Dr. Sardjito Hospital in January 1st, 2000 until October 31st, there were 40 cases of UTI. Two cases were excluded because of incomplete records, so that the case group consisted of 38 subjects.

TABLE 1. Characteristics of the study subjects

Variable	Case (N=38)	Control (N=109)	Total (147)
Gender			%
• Male	15	66	55.1
• Female	23	43	44.9
Age			
• < 5 years old	12	53	44.2
• > 5 years old	26	56	55.8
Nutritional status			
• Poor	3	5	5.4
• Fair	8	23	21.1
• Normal	23	73	65.3
• Overweight	4	8	8.2
Leukemia			
• ALL	34	93	86.4
• AML	4	16	13.6
Chemotherapeutic phase			
• Induction	21	46	45.6
• Reinduction	2	7	6.1
• Consolidation	5	44	33.3
• Maintenance	10	8	12.2
• Intensification	0	4	2.7
Neutropenia			
• Severe	13	32	30.6
• Moderate	4	25	19.7
• Normal	21	52	49.7

In TABLE 1, baseline characteristics of our study showed that the highest proportion of leukemia was acute lymphoblastic leukemia and the highest gender who had leukemia was boys. statistically significant risk factor of UTI in leukemia was gender female (with OR = 2.35 (95% CI: 1.10-5.00).

Multivariate analysis showed that gender female increased the risk 2.36 times compared to boys (TABLE 2).

TABLE 2. Risk factors of UTI (multivariate analysis)

Variable	OR	95% CI	P
Gender			
• Female	2.36	(1.08- 5.14)	0.03
• Male	1		

DISCUSSION

The difference of UTI prevalence depends on age, gender, race, and other factors. UTI prevalence in girls was around 3% and in boys was around 1%. UTI occurrence after chemotherapeutic use was reported around 5%.[17] The author tried to prolong the research duration to fulfill the sample size. Limitation on other predisposed factors such as anatomical and functional abnormality, phimosis, and constipation was aimed to be more focused on the leukemia patients themselves. Patients with neutropenia had a higher risk for septicemia caused by gram negative bacteria. Urinary tract is one of the port of entry of bacteria. Neutrophil has role of bacterial clearance in UTI.[18] So far, there was no study investigating neutropenia as risk factor of UTI. From the result of our study, neutropenia was not the risk factor of UTI occurrence. This result was contradicted with the result of previous research that suggested that patients with severe neutropenia had risk of infection, with OR 2.72 (95% CI: 1.72-4.28).[16] Other study found that infection in severe neutropenia was more common compared to moderate and mild neutropenia, where 32% occurred in UTI.[19] Pathogenesis of UTI is very complex. At initial phase of UTI, natural immunity has more important role compared to specific immunity, through diuresis mechanism.[18,20] Lehmbercher *et al.* explained that a small proportion

of infection occurred without any neutropenia.[14] This was caused by other treatment that stimulated changes in immune system, such as lymphocyte, natural killer cell, and non-adaptive immunity. Pathogenesis of UTI was known to occur through ascending mechanism and hematogenous mechanism. Usually, hematogenous widespread seldom occurred, except in neonates. Mechanism of urinary tract itself was to maintain the sterility of urine through urine acidity, unblocked free flow, mucosal barrier, and intact ureterovesical sphincter valve. The effect of antibiotics given in neutropenic fever may affect the elimination of bacteria causing UTI.[21] In neutropenic fever, comorbidity is a factor that has a role and related to treatment failure, severe infection, and death. By considering the presence of comorbidity factor in the treatment of children with neutropenic fever, children may be classified into at low risk and high risk of infection.[22] The Infectious Disease Society (IDSA) made a guideline for antibiotic administration in neutropenia patients at low risk and high risk.[23] The duration of antibiotic administration is determined by neutrophil count in peripheral blood. In neutropenic fever, if there was no identifiable infection after 3 day treatment and neutrophil count was >500/uL for 2 days and afebrile for 48 hours, antibiotics may be stopped.[22] According to National Comprehensive Cancer Network, in fever of unknown origin with neutrophil absolute count <500/uL, antibiotics should be given for 7-14 days.

In this study, age and nutritional status were not related to UTI. This is contradicted with previous studies that suggested that poor nutritional status increased the occurrence of UTI, compared to patients with good nutritional status.[24] Age less than 3 months with male gender and age more than 3 months for female were risk factors of UTI.[25] Risk of UTI in poor nutritional status is resulted from anatomical barrier damage, the decrease in cell-mediated immunity, the decrease in opsonization activity, the decrease in phagocytosis effect and vitamin A deficiency in patients who had poor nutrition.[24,26] Aside of that, poor nutritional status is an immunocompromized condition.

We found that age was risk factor for UTI. Females had higher risk of UTI, compared to males. This is comparable with previous study that suggested that females had higher risk of UTI compared to males, OR = 1.68 (95% CI: 1.18-2.38), p= 0.003.[27] Short urethra in females is one of the predisposing factors of UTI, therefore, UTI incidence in females is higher than in females.[20]

The most often bacteria causing UTI in leukemia is *E. coli* and Klebsiella. Several studies suggested that there was no difference in UTI etiology in leukemia and non-leukemia patients. *E. coli* and Klebsiella is a common bacteria in urine culture of UTI in leukemia.[9,10] Candida was yeast that causes UTI in this study. Predisposing factor of yeast infection is neutropenia, long-term antibiotic administration, and corticosteroid use.

The limitation of this study was in the analysis of antibiotics. In this study, it was not analyzed whether antibiotic administration on case group at the initial part of the study until urine culture affected the result of bacterial elimination. The prophylactic antibiotic in neutropenia may eliminate bacteria that causes UTI. Duration of antibiotic may have effect on the result of urine culture in neutropenic fever. Aside of that, UTI is affected by other predisposing factors. We also could not avoid the possibility of information bias, because medical records were often inaccurate.

CONCLUSION AND SUGGESTION

Based on the result of this study, it was concluded that neutropenia, age, and nitritional status were not risk factors of UTI in leukemia children. Gender is a risk factor of UTI in leukemia. This study still had several limitations, among others, the need to analysis on antibiotic administration in neutropenia as variables that may affect the result of the sudy. Other limitation was lack of studies investigating the relation between neutropenia and UTI, so that a prospective study is needed.

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