Original Article

Microbiological profiles and prognostic factors of infection mortality in febrile neutropenic children with malignancy

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Abstract

Background Post-chemotherapy febrile neutropenia results in high morbidity and mortality in children with malignancy. Many prognostic factors, such as microorganism patterns, as well as the use of antibiotics and antifungals can affect the outcomes. However, limited study is available in Indonesia.

Objective To determine the microbial profiles, antibiotic sensitivity, and other factors that influence mortality from febrile neutropenia in pediatric malignancies with infections.

Methods This retrospective cohort and descriptive study of 180 children with 252 episodes of neutropenic fever was done in Cipto Mangunkusumo Hospital, Jakarta, between 2015 and 2017. Medical history of possible predictive prognostic factors, including microorganism patterns and antibiotic sensitivity, were recorded. Prognostic factors were analyzed using multivariate logistic regression tests.

Results The most common bacteria was Gram-negative (541.5%), while *Candida sp.* was the most common fungal infection (82.5%). *Klebsiella sp.* was mainly sensitive to amikacin (85.71%), while *Pseudomonas aeruginosa* was sensitive to ceftazidime (75%), as well as amikacin and gentamicin (100% sensitivity in combination). *Staphylococcus sp.* was mainly sensitive to amoxi-clav and ampi-sulbactam (76.9%). Almost all fungal groups were susceptible to fluconazole, ketoconazole, voriconazole (80-100%). Prognostic factors that increased mortality risk were central venous cannulation (RR 1.947; 95%CI 1.114 to 3.402), wasting (RR 1.176; 95%CI 1.044 to 1.325), severe wasting (RR 1.241; 95%CI 0.975 to 1.579), and hematologic malignancies (RR 0.87; 95%CI 0.788 to 0.976).

Conclusion Central venous cannulation and wasting are significant prognostic factors of increased mortality in children with febrile neutropenia. Gram negative bacteria along with *Candida sp.* is the most common pathogen in such condition. **[Paediatr Indones. 2021;61:283-90 ; DOI: 10.14238/pi61.5.2021.283-90].**

Keywords: *febrile neutropenia; mortality; prognostic factors; malignancy; microbial profile*

Life expectancy in pediatric patients with malignancy is now much higher, as children receiving chemotherapy increasingly get adequate supportive therapy. However, complications due to the chemotherapy have not been well-addressed. One of the most frequent and serious complications is febrile neutropenia (FN).[1] Febrile neutropenia increases mortality and reduces the efficacy of chemotherapeutic agents by necessitating delays in the chemotherapy schedule and decreased dosage of chemotherapeutic drugs. Although it has dropped dramatically in recent years, the mortality rate of febrile neutropenia remains high, comprising approximately 5% of patients with solid tumors and 11% of all hematologic malignancies. Gram-negative bacterial infections lead to three times more deaths than Gram-positive infections.[1,2]

The Rondinelli score can be used as an instrument to determine the prognosis of febrile neutropenic patients by considering morbidity factors that are predicted to significantly influence the outcomes, such

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as antimicrobial resistance, microbial pattern, fungal infections, and nutritional status.[3-5] Resistance to antimicrobial agents leads to difficulty in controlling the microbes and consequently to an outcome that aggravates bacteremia in febrile neutropenic patients. Therefore, thoughtful consideration is needed in order to give the appropriate initial empirical therapy. These considerations include the bacterial etiology spectrum in neutropenic fever, tumour (malignancy) type, and patients' blood culture results to identify resistance patterns to antimicrobials given.[2,6]

Dr. Cipto Mangunkusumo Hospital, Jakarta, follows guidelines for administering antibiotics based on the classification of febrile neutropenia.[7] In Indonesia, few studies have identified microbial patterns, antimicrobial resistance patterns, and other prognostic factors for outcomes of febrile neutropenia patients with malignancy. As such, our study was done with the aim of providing information on optimal treatment for febrile neutropenia management, including empirical antimicrobial therapy in febrile neutropenic patients.

Methods

This retrospective cohort study was done to determine the prognostic factors of mortality outcome and microorganism patterns in pediatric inpatients with malignancy who experienced febrile neutropenia as a secondary outcome. Subjects were treated in the pediatric ward and pediatric intensive care unit of Dr. Cipto Mangunkusumo Hospital, Jakarta.

We searched for data from medical records at the Kiara building and central medical records from patients treated from January 1, 2015 to December 31, 2017 at the Hematology-Oncology Division, Department of Child Health, Universitas Indonesia Medical School/Dr. Cipto Mangunkusumo Hospital, Universitas Indonesia. The inclusion criteria were all pediatric patients aged 1 to 18 years, admitted to the 3rd class pediatric ward and the intensive care unit at Dr. Cipto Mangunkusumo Hospital, and who had been diagnosed with febrile neutropenia with malignancy between 2015 and 2017. The diagnosis of febrile neutropenia was made by clinical and laboratory criteria, with or without blood culture as additional criteria. We also defined isolated culture as non-blood culture that was isolated from specific site, e.g. urine,

stool, or sputum to clarify the port d'entree. We only included patients with malignancy-related febrile neutropenia, while excluding those without > 1 blood cultures (or isolated cultures) sampling and those with incomplete medical records. There were 252 episodes of febrile neutropenia from 180 pediatric patients who met the inclusion criteria.

Ethical clearance was obtained from Committee of Medical/Health Research Ethics FKUI/RSCM.

We used Rondinelli score as an instrument to determine the prognosis of febrile neutropenic pediatric patients.[5] Possible prognostic factors of outcomes including age (< 5 years and >5 years), central venous catheter insertion, focal infection, fever, hemoglobin level, acute respiratory tract infection. The patient was classified as high risk with score > 9, moderate with >5.5 to 9 and low risk with < 5.5. Furthermore, we also analyzed, systemic fungal infection, nutritional status, absolute neutrophil count (ANC), total number of monocytes, tumour type, and chemotherapy regimen as the possible factors that contribute to outcome. All data were recorded and analysed using multivariate logistic regression test. We also obtained descriptive data regarding the use of antibiotics, antifungals, and microorganism patterns.

Results

A total of 180 subjects with 252 febrile neutropenic episodes were included in the data analysis (**Table 1**). There were more male (57.8%) than female patients (42.2%). Most patients (71.1%) experienced only one episode of febrile neutropenia, followed by 38 subjects with two episodes (21.1%), 10 subjects with 3 episodes (5.6%), and four subjects with 4 episodes (2.2%). The most prevalent malignancy type was hematologic (73.9%), of which lymphoblastic leukemia was the most common (48.1%), followed by acute myeloblastic leukemia (36%). Approximately a quarter of patients had solid tumors (26.1%). The types of chemotherapy, severe and mild, were similar, with 135 (53.6%) and 117 (46.4%) episodes, respectively.

Bacteremia was found in 33 episodes (13.8% of blood cultures), and negative results were obtained in 213 episodes (84.5%). Patients who underwent cultures from urine, feces, sputum, and swab had positive results in 160 episodes (72.7% of isolated cultures) compared

Table 1. Patients' characteristics by number of subjects or number of episodes

Characteristics	Number of subjects (n=180)	Number of episodes (n=252)
Gender, n (%)		
Male	104 (57.8)	
Female	76 (42.2)	
Total episodes per subject, n (%)		
1 time	128 (71.1)	
2 times	38 (21.1)	
3 times	10 (5.6)	
4 times	4 (2.2)	
Tumor type, n (%)		
Solid	47 (26.1)	
Hematologic malignancy	133 (73.9)	
Chemotherapy category, n (%)		
Mild		117 (46.4)
Severe		135 (53.6)
Blood culture, n (%)		
Positive		334 (13.1)
Negative		213 (844.5)
No data/not performed		6 (2.4)
Isolated culture, n (%)		
Positive		160 (63.5)
Negative		60 (23.8)
No data/not performed		32 (12.7)
Fungal culture, n (%)		
Positive		23 (8.7)
Negative		87 (34.5)
No data/not performed		142 (56.3)
Outcomes, n (%)		
Survived	136 (75.5)	
Died	44 (24.4)	
No. of episodes survived, n (%)		208 (82.5)

to negative results in 60 episodes (23.8%). Such cultures were not performed for the remaining episodes. Positive focal infection was found in 1605 (72.7% of isolated cultures) episodes. Fungal blood cultures were examined in 110 episodes (43.6%), of which 23 episodes (21% of blood cultures) were positive.

Majority of the patients had episodes of low (<5.5) Rondinelli score (data not shown). Rondinelli score predicted FN mortality risk with younger age, central venous catheter, evident port d'entrée, fever, anemia, and upper respiratory tract infection as mortality risk factors. For the mortality outcome, 75.5% of subjects survived, but the rest died. In terms of episodes, subjects survived 208 episodes (82.5%). The most common cause of death was hematologic malignancy, such as acute myeloid leukemia (AML) (50%), acute lymphoblastic leukemia (ALL) (34.1%), and lymphoma (4.54%), while solid tumors led to death in 5 subjects (11.3%). Deaths were mostly due to severe sepsis (84%) or respiratory failure (6.8%), and only rarely due to hypovolemic shock and intracranial bleeding (4.5%).

Table 2 shows that from 33 episodes of febrile neutropenia with positive blood cultures, Gram-negative bacteria predominated slightly, consisting of *Klebsiella pneumoniae* (17.6%), *Pseudomonas aeruginosa* (11.8%), and other Gram-negative bacteria (2.9% each). Blood cultures with Gram-positive bacteria consisted of *Staphylococcus aureus* (17.6%), *Staphylococcus epidermidis* (14.7%), as well as *Staphylococcus saprophyticus* and alpha-hemolytic Streptococcus (5.9% each). Bacteremia with Gram-negative bacteria was seen in 17 of 33 episodes (51.5%) and bacteremia with Gram-positive bacteria was found in 16 of 33 episodes (47.1%).

Fungal blood culture was carried out in 100 febrile

Table 2. Pathogen profiles

Variables	n
Blood culture microorganisms, n=33 episodes	
Gram-negative bacteria	18
Acinetobacter lwoffii	1
Acinetobacter baumanii	1
E. coli	1
Enterobacter cloacae	1
Klebsiella oxytoca	1
Klebsiella pneumoniae	6
Kocuria kristinae	1
Pseudomonas aeruginosa	4
Salmonella sp	1
Serratia liquefaciens	1
Gram-positive bacteria	15
Staphylococcus aureus	6
Staphylococcus epidermidis	5
Staphylococcus saprophyticus	2
Streptococcus alpha-hemolytic	2
Fungal culture, n=23	
Candida albicans	11
Candida parapsilosis	5
Candida glabarata	1
Rhidotorulla	1
Candida krucei	1
Candida tropicalis	3
Malasezia furfur	1
Isolated culture, n=160	n (%)
Acinetobacter baumanii	6 (3.8)
Acinetobacter iwofii	7 (4.4)
Acinetobacter sp	1 (0.6)
Candida albicans	4 (2.5)
Candida tropicalis	4 (2.5)
E. coli	36 (22.5)
E. faecalis	3 (1.9)
Enterobacter aerogenes	3 (1.9)
Enterobacter cloacae	4 (2.5)
Enterococcus faecalis	22 (13.7)
Enterococcus faecium	6 (3.8)
Enterococcus sp.	1 (0.6)
Klebsiella pneumoniae	23 (14.3)
Klebsiella oxytoca	5 (3.1)
Proteus mirabilis	3 (1.9)
Proteus vulgaris	6 (3.8)
Pseudomonas aeruginosa	13 (8.1)
Staphylococcus epidermidis	8 (5)
Staphylococcus aureus	4 (2.5)
Staphylococcus saprophyticus	1 (0.6)

neutropenia episodes (43.6%), of which 23 episodes (24.5%) were positive. *Candida albicans* ranked first as the most common fungal culture (47.8%), followed by *Candida parapsilosis* (21.7%), and *Candida tropicalis* (13%). *Malasezia furfur*, *Candida glabarata*, *Candida krucei*, and Rhidotorulla were the least common fungal species found (in 1 subject each; 4.3%).

From the 160 episodes with positive isolated culture, *E. coli* was most common (36 episodes; 22.5%), followed by *E. faecalis* (15.6%), *K. pneumoniae* (14.14%), and *Pseudomonas aeruginosa* (8.1%). Meanwhile, Gram-positive bacteria found in patients mostly consisted of *Staphylococcus epidermidis* (4.4%), *Staphylococcus aureus* (2.5%), and *Staphylococcus saprophyticus* (0.6%). For fungal infection, *Candida albicans* and *Candida tropicalis* were most common. Gram-negative bacteria were predominated by *E. coli* in isolates derived from urine culture, and *E. faecalis* was the second-highest and obtained in isolates from stool culture, along with *K. pneumoneae*. In addition, Gram-positive bacteria were mostly found in skin wound swabs.

Table 3 shows the multivariate analysis for the most possible prognostic factors. A statistically significant improvement in survival was revealed in patients without central venous catheters (RR 1.947; 95%CI 1.114 to 3.402; P=0.0001). In addition, patients who had good nutritional status were more likely to survive compared to severely wasted patients (RR 1.241; 95%CI 0.975 to 1.579), wasted patients (RR 1.176; 95%CI 1.044 to 1.325), overweight patients (RR 1.183; 95%CI 0.679 to 4.840), and obese patients (RR 0.907; 95%CI 0.853 to 0.963) (P=0.031). Furthermore, patients with hematologic malignancy were less likely to survive compared to patients with solid tumours (RR 0.877; 95%CI 0.788 to 0.976; P=0.049). The RRs of the other possible prognostic factors are shown in **Table 3** but no significant differences were revealed in age at diagnosis, focal infection, fever, acute upper respiratory tract infection, or chemotherapy type (P>0.05 for all).

Discussion

A total of 252 febrile neutropenic episodes occurred in 180 subjects in our study. There were more male than female patients. Additionally, most patients experienced only one neutropenic fever event. The most common tumor type was hematologic malignancy; 57.1% of the patients suffered from ALL. It is in accordance with similar study in Turkey.[3] The highest mortality outcome in our study was found in hematologic malignancies, such as AML (50%), followed by ALL (34.1%). However, the most common cause of mortality was

Table 3. Multivariate analysis of possible prognostic factors

Clinical variables	Outcomes, n (%)		RR (95% CI)	P value
	Survived (n=208)	Died (n=44)		
Age at cancer diagnosis, n (%)			1.007 (0.897 to 1.132)	0.902
> 5 years	125 (82.8)	26 (17.2)		
< 5 years	83 (82.2)	18 (17.8)		
Central venous catheter			1.947 (1.114 to 3.402)	0.0001**
Present	7 (43.8)	9 (56.3)		
Absent	201 (85.2)	35 (14.8)		
Focal infection			1.044 (0.933 to 1.169)	0.460
Absent	93 (84.5)	17 (15.5)		
Present	115 (81.0)	27 (19.0)		
Fever			1.115 (0.999 to 1.243)	0.083
<38.5ºC	65 (89.0)	8 (11.0)		
>38.5ºC	143 (79.9)	36 (20.1)		
Acute upper respiratory tract infection			0.963 (0.852 to 1.089)	0.565
Absent	152 (81.7)	34 (18.3)		
Present	56 (84.8)	10 (15.2)		
Nutritional status				0.031**
Normal	97 (90.7)	10 (9.3)		
Severely wasted	9 (73.1)	7 (26.9)	1.241 (0.975 to 1.579)	
Wasted	84 (77.1)	25 (22.9)	1.176 (1.044 to 1.325)	
Overweight	2 (50.0)	2 (50.0)	1.183 (0.679 to 4.840)	
Obese	6 (100.0)	0 (0.0)	0.907 (0.853 to 0.963)	
Tumor type			0.877 (0.788 to 0.976)	0.049**
Solid	52 (91.2)	5 (8.8)		
Non-solid	156 (80.0)	39 (20.0)		
Chemotherapy type			0.951 (0.848 to 1.068)	0.392
Mild	94 (79.7)	23 (19.7)		
Severe	114 (85.1)	21 (15.6)		

sepsis, accounting for 84%.

These characteristics were in accordance with other studies from developing countries, namely Turkey, Egypt, and India.[8-10] Males may have more malignancies due to hormonal influence, gene expression, epigenetics, and immune status making them more vulnerable to malignancy. Female innate and adaptive immunity is better in fighting pathogens, including malignant cells. However, females are more susceptible to autoimmune disease.[11] The tumor type in our study was similar to other studies which noted ALL as the most common type of malignancy in pediatric patients.[8,9] A previous study found that 74% deaths in AML were due to sepsis, and AML mortality was 52.9%, which was in agreement with the Department of Child Health Cancer Registry of 62%.[12]

Positive blood cultures were found in only 33 of 252 episodes (13.1%), possibly due to suboptimal sampling techniques. The blood culture specimens were sometimes obtained after the first dose of empiric antibiotic administration. Furthermore, the minimum blood volume sample needed to generate positive culture results in pediatric patients with febrile neutropenia is still unclear and often leads to a false-negative result.[11] A similar study in Iran stated that blood cultures were only positive about 3% of the time for such reasons.[13] Other study carried out in Dr. Cipto Mangunkusumo Hospital in past years also found that bacteremia ranged from 12 to 17%.[14]

The microorganism frequency changes over time. Different results from blood culture can occur in different countries or even in different areas in the same country. In general, Gram-positive bacteria were most common from year 1996 to 2004, and over time, Gram-negative bacteria were found to be more prevalent between 2000 and 2004. A number of studies have varied results, with more Gram-positive bacteria, at 68% to 70%. In contrast, other studies discovered

that Gram-negative bacteria were more prevalent, at 50% to 85%.[9,15] From our blood cultures, the number of Gram-negative bacteria was almost the same as Gram-positive bacteria, in accordance with a study by Ozdemir *et al*.[3]

The high number of *Candida albicans* species in our subjects was similar to other studies in children with malignancy, with *C. albicans* predominating in many institutions as well as increasing *C. krusei* and *C. glabrata*.[3,16,17] Nevertheless, we found only 1 positive each for *C. krusei* and *C. glabrata*. An increase in systemic invasive infection due to fungi were suspected due to: (1) intensive chemotherapy and steroid use; (2) long-term neutropenia; (3) the use of broad-spectrum antibiotics; (4) the use of a central venous catheter, and; (5) more advanced techniques to identify fungal infection.[3]

Antibiotics for *Staphylococcus sp.* and *Streptococcus sp.* group with the highest sensitivity were amoxi-clav as the first line and ampi-sulbactam as the second line, followed by vancomycin and tigecycline as the third line. The third line was administered only as definitive therapy. This finding was consistent with the antibiotic sensitivity in Dr. Cipto Mangunkusumo Hospital obtained from blood culture performed in the pediatric wards. *Klebsiella sp.* had good sensitivity with amoxi-clav as the first line, amikacin as the second line, and tigecycline as the third line. Nevertheless, empirical oral amoxi-clav was only given if the clinical symptoms improved, followed by ANC increase in low-risk patients, due to the number of high risk patients in our center.[1]

In addition, amikacin as the second line, e.g. for persistent fever > 5 days or progressive clinical deterioration, was the most common antibiotic used in combination with third-generation cephalosporin. *Pseudomonas sp.* had high sensitivity to ceftazidime at around 75% with amikacin, and nearly 100% with gentamycin. Both combinations were frequently used in this study. Based on antibiotic sensitivity data, our internal paediatric guideline for FN can still be implemented specifically for urinary tract infection, which was generally due to *E. coli, P. aeruginosa*, or *K. pneumoniae*. Aside from ceftazidime, other antibiotics that can be administered include oral amoxi-clav, ampicillin-sulbactam, carbapenem group, or a combination between ceftazidime and amikacin. For pneumonia, ceftazidime together with aminoglycoside or carbapenem, can be the choice for empirical therapy. *Staphylococcus aureus* often causes skin infection, so the use of amoxi-clav and ampicillin-sulbactam can be considered as empirical therapy in such cases.

Even though the majority of FN episodes in this study were categorized as low risks, ceftazidime nevertheless was the most used. In accordance to *Indonesian Pediatrics Society* (IPS) recommendation, intravenous antibiotics are preferred because of: (1) low observed level of education, (2) low observed level of hygiene, and, (3) potentially inadequate care at home.[18] The absence of care providers, limited transportation, and accessibility of patients' homes to medical facilities also played roles in patient admission, which in turn made intravenous antibiotics the preferred agents.

The fungi had an overall good sensitivity using the azole and amphotericin B groups. Fluconazole was most widely used due to: (1) the same effectiveness as amphotericin B for most pathogens; (2) minimal adverse reactions; (3) availability, and; (4) easier administration technique. According to a past study, the mortality rate of febrile neutropenia patients receiving fluconazole was lower than amphotericin B, especially for those infected with *Candida sp*.[19] In contrast, the use of amphotericin B is more effective for Aspergillosis and Cryptococcus infections, but we found no infection from either fungal species. Therefore, fluconazole was an appropriate treatment both prophylactically and definitively. Antifungal administration in this study began when the fever duration was 7 days.

In our study, the use of central venous catheters was associated with nearly twice the risk of death for febrile neutropenia patients. (RR 1.947; 95%CI 1.114 to 3.402: P=0.0001). The use is closely related to central line-associated bloodstream infection (CLABSI), defined as a blood flow infection that arises within 48 hours after the insertion of a central venous catheter, confirmed by laboratory findings, and no other site of infection. Non-tunnelled central venous catheter that was used most frequently in this study was at greater risk of bacterial contamination from the exit site to intravascular sites. Bacteria that are often found in CLABSI are Gram-positive bacteria (coagulase-negative Staphylococcus, Enterococcus, Staphylococcus aureus), and Gram-negative bacteria

(Klebsiella, Enterobacter, Pseudomonas, *E. coli*, Acinetobacter), in addition to Candida sp. group.[20]

Other studies have reported that patients with central venous catheters had increased risk of severe infections that lead to death. The use has been closely associated with an increased frequency of fungal infections.[20-22] Fungal infections prolonged the duration of febrile neutropenia, delayed elevation of neutrophil levels and led to 50% of deaths in high-risk febrile neutropenia patients.[20] However, the high-risk use of central venous catheter for the mortality outcome in this study is still unclear in febrile neutropenia patients who also had systemic organ disturbance, including in the circulatory system. This was supported by less than 1% of all episodes with the insertion of a central venous catheter at the beginning (cell site). Nevertheless, most patients with central venous catheters died >24 hours after catheter insertion. Thus, the use of a central venous catheter can be considered as one of the factors that can escalate mortality.

Wasted and severely wasted patients, which comprised the majority of study subjects, potentially had higher risk of mortality compared to those with other nutritional statuses. This result was consistent with previous studies conducted in Yogyakarta, Indonesia, and Italy, which stated that malnutrition increased the incidence of infection and mortality. Malnourished children have natural and adaptive immune defects, which in turn inhibit complement, as well as reduce lymphocyte counts and macrophage activity. Additionally, malnutrition causes hematopoiesis, anemia, leukopenia, significant decreases in bone marrow, including IL-6 and TNF-α production, as well as hormonal disturbances.[23,24] Nevertheless, we need to consider the wide confidence interval of the nutrition groups relative risk and seemingly protective effect of obesity as the result of unbalanced numbers of subjects compared to their normal weight counterpart. Therefore, the RR needed to be interpreted carefully.[3]

Continuing that point, our study had several limitations. The available data was very diverse, and some data could not be retrieved due to incomplete medical records or missing information. These missing data, such as fungal blood culture, blood culture, antibiotic used for treatment, and other prognostic factor data could have been confounding factors or led to information bias. Therefore, future studies should be performed prospectively in order to obtain complete data.

The most prevalent microbes found in blood culture were Gram-negative bacteria. The most common fungi in our subjects were *Candida sp.* Empirical antibiotics most often used were anti-pseudomonal in combination with aminoglycosides, based on antibiotic sensitivity patterns in Dr. Cipto Mangunkusumo Hospital. The prognostic factors that increased the mortality outcome were the use of central venous catheter, poor nutritional status (wasted).

Conflicts of Interest

None declared.

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