PREVALENCE OF PATHOGENS IN PEDIATRIC CANCER PATIENTS WITH FEBRILE NEUTROPENIA

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Abstract. Febrile neutropenia (FN) is an important clinical problem in pediatric cancer patients who have been treated with chemotherapy. This study set forth to investigate the characteristics of FN, the sources of infection, and the prevalence of causative agents in pediatric cancer patients with FN. This retrospective chart review was conducted in pediatric cancer patients under 15 years of age who developed an episode of FN and who were treated at the Department of Pediatrics, Siriraj Hospital (Bangkok, Thailand) during the January 2005 to September 2013 study period. There were 214 episodes of FN from 179 patients. Median temperature at diagnosis was 38.9°C (range: 38.3-41). Of all FN episodes, 44.4% had initial absolute neutrophil count (ANC) <100 cell/mm^3, and 10.8% had identifiable causes of infection. Respiratory tract was the most common site of infection, and influenza virus was the most prevalent identifiable organism. Septicemia occurred in 5.61% of cases, and the most common type of pathogen was gram-positive bacteria. A majority of cases (77.5%) responded well to initial empirical antibiotic treatment. Two patients (0.93%) died from serious infection. Good response to treatment and low mortality was observed among the pediatric cancer patients with FN that were included in this study. Laboratory evaluation for viral pathogen, especially in patients with signs and symptoms of respiratory tract infection, should be strongly considered. A shift in tendency from gram-negative to gram-positive bacteria as the common pathogens in bacteremia is also emphasized.

Keywords: febrile neutropenia, pediatric cancer patients, chemotherapy, pathogens

INTRODUCTION

Febrile neutropenia (FN) is an important clinical problem in pediatric cancer patients that are receiving chemotherapy. These patients can develop severe infections without typical signs and symptoms. Physicians have to be aware of the risk of severe infection, the special diagnostic methods, and the intensive antimicrobial treatment that are required for management of pediatric cancer patients with FN. Patients who present with febrile neutropenia may have a variety of clinical outcomes (Freifeld *et al*, 2011). Most patients receive broad-spectrum empirical antibiotic treatment and survive without complications. However, a minority of patients may develop serious infection or experience other life-threatening medical events that result in death. Febrile neutropenia occurred in 10-50% of patients with non-hematologic malignancies and in 80% of those with hematologic malignancies (Klastersky, 2004). These patients

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developed FN-related fever after 1 or more courses of chemotherapy. Most of those patients had no identifiable source of infection. Clinically identified cause of infection was found in only 20-30% of febrile neutropenia episodes. The common sites of tissue-based infections included the intestinal tract, lung, and skin. Bacteremia was found in 10-25% of all patients, with most episodes occurring in the setting of prolonged or profound neutropenia [absolute neutrophil count (ANC) <100 /mm^3] (Bodey *et al*, 1966; Ramphal, 2004; Rosenberg *et al*, 2006).

Over the past 40 years, there has been significant fluctuation in the epidemiologic spectrum of causative pathogens isolated from the blood of febrile neutropenia patients. During the 1960s and 1970s, gram-negative pathogens predominated. However, during the 1980s and 1990s, gram-positive organisms became more common (Zinner, 1999; Wisplinghoff *et al*, 2003), due to the increasing use of indwelling venous catheters, which can cause colonization and entry of gram-positive normal skin flora (Zinner, 1999; Hughes *et al*, 2002).

According to some reports, the most common pathogens isolated from blood at many centers were coagulase-negative staphylococci and Enterobacteriaciae, such as *Enterobacter* species, *Escherichia coli*, and *Klebsiella* species. In contrast, non-fermenting gram-negative rods, such as *Stenotrophomonas* species and *Pseudomonas aeruginosa*, were isolated less often. While infections from drug-resistant gram-negative bacteria species were increasing in febrile neutropenia patients in some centers, the epidemiologic trend toward gram-negative organism predominance still remained in neutropenia patients which were the same as previous studies in Thailand (Anunnatsiri *et al*, 1998; Chen *et al*, 2004; Rosenberg *et al*, 2006; Laoprasopwattana, *et al*, 2007; Oliveira *et al*, 2007; Cattaneo *et al*, 2008; Sanboonrat *et al*, 2009; Wangirapan *et al*, 2012; Limvorapitak and Khawcharoenporn, 2015). There is limited data on the characteristics of FN, the sources of infection, and the pathogens that cause FN in pediatric cancer patients in Thailand.

Accordingly, the aim of this study was to investigate the characteristics of febrile neutropenia, the sources of infection, and the prevalence of causative agents in Thai pediatric cancer patients with febrile neutropenia.

MATERIALS AND METHODS

This retrospective chart review was conducted in pediatric cancer patients under 15 years of age who developed an episode of FN and who were treated at the Department of Pediatrics, Siriraj Hospital (Bangkok, Thailand) during the January 2005 to September 2013 study period. Siriraj Hospital is Thailand's largest university-based national tertiary referral center. The study protocol was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (approval no. Si493/2014).

Two hundred and fourteen consecutive admissions for episodes of febrile neutropenia in 179 pediatric cancer patients were included in this study. Data obtained from medical records included gender, age, underlying cancer diagnosis, duration of neutropenia, source of infection, causative agents, type of antibiotics used, granulocyte colony-stimulating factor (G-CSF) use, presence of indwelling catheter, interval since last chemotherapy, FN-related complications, other infection-related factors, and patient outcome. Febrile neutropenia was defined as an oral temperature >38.5°C, or two consecutive readings of >38.0°C for 2 hours and an ANC <500/mm^3 or an ANC that is expected to fall below 500/mm^3 (de Naurois *et al*, 2010). All patients were immediately hospitalized and received empirical antibiotics.

Statistical analysis

Data were analyzed using descriptive statistics, and PASW Statistics for Windows version

18.0 (IBM, Armonk, NY) was used for all data analyses. Data are presented as number and percentage, mean ± standard deviation, or median and range. Data were compared using chi-square test or Fisher's exact test, as appropriate. Correlations between variables were analyzed by Spearman's rank analysis. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Of 214 episodes of febrile neutropenia in 179 patients, 130 episodes (60.7%) occurred in patients with hematologic malignancies and 84 episodes (39.3%) developed in patients with non-hematologic malignancies. Demographic and clinical characteristics of FN patients are shown in Table 1. The source of infection could be identified in 37.4% (80/214) of FN episodes. The most common source was respiratory tract infection (46.3%; 37/80), which was identified by nasopharyngeal wash. Influenza infection was detected in 11 of 37 (29.7%) FN episodes with respiratory tract infection. Two episodes of oral candidiasis were found in the hematologic malignancies group.

Sources of infection, causative agents, and initial antibiotics used in febrile neutropenia patients are shown in Table 2. A majority of cases (77.5%) responded well to initial empirical antibiotic treatment. The antibiotics in 46 episodes (21.5%) were switched to higher broad-spectrum. Of those 46 episodes, 35 (16.3%) were hematologic malignancies and 11 (5.2%) were non-hematologic malignancies. Forty-three (20.1%) FN episodes required a switch in antibiotics due to the identification of additional source(s) of infection.

The most common additional antibiotic used was metronidazole, which was associated with perianal abscess. The median duration from the last day of chemotherapy to the day at diagnosis of FN was 7 days (range: 0-66). At initial diagnosis, the median temperature of FN patients was 38.9°C (range: 38.3-41). The patients who had ANC <100 cells/mm^3 on day 3 had a significantly longer mean duration of fever than those with ANC on day 3 ≥100 cells/mm^3 (4.75±1.65 *vs* 2.88±0.68 days; *p*=0.01). The characteristics of FN episodes are given in Table 3. Patients with ANC on day 3 <100/mm^3 tended to have a higher likelihood of switching antibiotics than those with ANC ≥100/mm^3 (OR=4.51; 95% CI: 2.11-9.58).

Table 1
Demographic and clinical characteristics of patients with febrile neutropenia (*N*=214).

Parameters	*n* (%)
Male gender	128 (59.8)
Age (yr), median (range)	6 (1-14)
Type of malignancy	
Hematologic malignancies	130 (60.7)
ALL	75 (35.0)
ANLL	27 (12.6)
Lymphoma	26 (12.2)
Others	2 (0.9)
Non-hematologic malignancies	84 (39.3)
Neuroblastoma	19 (8.9)
Osteosarcoma	13 (6.1)
Rhabdomyosarcoma	12 (5.6)
Brain tumors	12 (5.6)
Others	28 (13.1)
Initial ANC (cell/mm^3)	
<100	95 (44.4)
100-499	86 (40.2)
>500	33 (15.4)
ANC at 72 hours after diagnosis of FN (*n*=209)	
<100	62 (29.0)
100-499	63 (29.4)
>500	84 (39.2)

ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; ANLL, acute non-lymphoblastic leukemia; FN febrile neutropenia.

Table 2
Sources of infection, causative agents, and initial antibiotics used in febrile neutropenia patients (*N*=214).

Characteristics of infection	Frequency (%)
Sources of infection	
Unidentified	134 (62.6)
Respiratory tract infection	37 (17.3)
Gastroenteritis	22 (10.3)
Skin infection	10 (4.7)
Urinary tract infection	6 (2.8)
Mucositis	5 (2.3)
Causative agents	
Unidentified	191 (89.2)
Gram-positive bacteria	8 (3.7)
Coagulase-negative *Staphylococcus*	5 (2.3)
Coryneform bacteria	1 (0.5)
Bacillus species	1 (0.5)
Micrococcus species	1 (0.5)
Gram-negative bacteria	4 (1.9)
Klebsiella pneumoniae	1 (0.5)
Escherichia coli	1 (0.5)
Pseudomonas aeruginosa	1 (0.5)
Non-fermenting gram-negative bacilli	1 (0.5)
Virus	
Influenza virus	11 (5.1)
Oral candidiasis	2 (0.9)
Initial antibiotics	
Ceftazidime + gentamicin	165 (77.1)
Piperacillin/tazobactam	25 (11.7)
Meropenem + amikacin	9 (4.2)
Others	15 (7.0)

Initial temperature, ANC on day 1, ANC on day 3, identification of the source of infection, and recurrence of fever were not significantly different between hematologic and non-hematologic malignancies or between hematologic malignancy patients in remission versus those not in remissions (data was not shown). Patients who received G-CSF had significantly shorter mean duration of treatment than those who did not receive G-CSF (3.8±0.8 *vs* 1.8±1.3 days; $p<0.01$). Causative organisms could be identified significantly more often in patients with temperature ≥40°C than in those with temperature <40°C (OR=4.34; 95% CI: 1.37-12.96).

The median duration of treatment in both the hematologic and non-hematologic malignancies groups was 7 days (range: 3-31 *vs* 2-21; $p=0.42$). Two patients (0.93%) died during treatment. One patient suffered a relapse of

acute lymphoblastic leukemia (ALL) and received meropenem plus amikacin since the beginning of the treatment due to clinical signs of sepsis. That patient expired on day 19 of treatment. The other patient suffered a relapse of acute myeloid leukemia and was treated with piperacillin/tazobactam that was later switched to meropenam plus amikacin due to unresponsiveness to treatment. That patient developed septic shock and died on day 31 of treatment. All cultures in the both patients were negative, and neither had central line placement.

A statistically significant correlation was observed between patients with underlying relapsed hematologic malignancies and death from FN (p=0.02). Eleven episodes of FN occurred in patients who had indwelling catheters, as follows: central venous catheter (4 episodes; 1.87%); urethral catheter (6 episodes; 2.8%); and, endotracheal tube intubation (1 episode; 0.46%). No septicemia was observed in any of the 11 episodes that involved indwelling catheter. G-CSF was used in 40 episodes (18.7%), as follows: 14 (6.5%) episodes among hematologic malignancies and 26 (12.2%) episodes among non-hematologic malignancies. The relationships between G-CSF use and type of causative organism are shown in Table 4. Having hematologic malignancies, having relapse of refractory diseases, and the ability to identify the source of infection were not significant predictors of mortality from FN.

DISCUSSION

In this study, FN occurred 1.5 times more often in hematologic malignancies than in solid tumors. This could be due to more aggressive and longer duration chemotherapy in hematologic malignancies, as compared to intensive pulse treatment in solid tumors. Moreover, the bone

Table 3
Characteristics of febrile neutropenic episodes.

Characters	Mean±2SD	Median (range)
Initial temperature (˚C)	39±0.6	38.9 (38.3-41)
Initial ANC (cell/mm^3)	223.1±250.4	110 (0-990)
ANC at 72 hours after diagnosis (cell/mm^3)	1,662.9±4,065.9	320 (0-33,530)
Duration of fever (days)	4±3.86	3 (1-23)
Duration of neutropenia (days)	7.33±7.78	5 (2-59)
Duration after last chemotherapy (days)	8.87±8.67	7 (0-66)

ANC, absolute neutrophil count.

Table 4
Relationship between granulocyte colony-stimulating factor (G-CSF) usage and type of causative organism.

G-CSF usage	Causative organisms (%)			
	Virus	GPB	GNB	Fungus
Yes (n=40), n (%)	1 (0.5%)	3 (1.4%)	5 (2.3%)	2 (0.9%)
No (n=174), n (%)	10 (4.7%)	7 (3.3%)	8 (3.7%)	0 (0.0%)

GNB, gram-negative bacteria; GPB, gram-positive bacteria.

marrow reserve in hematologic malignancies is usually adversely affected by the underlying disease, especially in those who are not in a remission state. A previous study reported that bacteremia accounted for 35% of infections among FN patients with hematologic malignancies and for 20% of infections among FN patients with solid tumors (Yadegarynia *et al*, 2003). That same study found that infections occurring at specific sites (*eg*, pneumonia) or polymicrobial infections were associated with higher rates of mortality. Another study reported that a majority of patients with FN did not have a microbiologically confirmed infection, but those who did were at risk for developing overwhelming sepsis (Hakim *et al*, 2009). Among the patients in this study, the causative agents were identified in only 23 of 214 FN episodes (10.8%).

Laboratory-confirmed viral etiology was established in 5.1% of infections. This finding is similar to previously reported rates of 5-8% for FN episodes with viral etiology (Lehrnbecher *et al*, 2004; Castagnola *et al*, 2007). This finding also highlights the importance of including investigation of viruses as part of FN work-up. The most common site of identifiable infection in our FN episodes was respiratory tract infection, and influenza virus was the only type of virus isolated. This is concordant to the increased prevalence of influenza infection in Thailand during the year 2009-2013 compared to that in Thailand during the year 2004-2008 (Suttachana, 2012).

Regarding bacterial infection, we found bacteremia to be the most common microbiologically documented type, with gram-positive bacteria being the predominant pathogens. Previous studies reported gram-negative bacteria to be the major cause of bacteremia. However, over the past decade, there has been a shift in predominance from gram-negative to gram-positive bacteria in both pediatric and adult patients (Hann *et al*, 1997; Ariffin *et al*, 2002; Wisplinghoff *et al*, 2003; Yadegarynia *et al*, 2003; Lehrnbecher *et al*, 2004; Kamana *et al*, 2005; Viscoli *et al*, 2005; Castagnola *et al*, 2007).

The bacterial pathogens that cause infection in pediatric patients with FN have recently begun to change in the United States and Europe, where the incidence of gram-positive pathogens has steadily increased. In the United States, 60-70% of bacteremia with a single identified organism was caused by gram-positive cocci – mainly coagulase-negative Staphylococci, Enterococci, or *Staphylococcus aureus*. The cause of this change has not been clearly identified and is probably multifactorial. Possible explanations include aggressive chemotherapeutic regimens that cause more severe mucositis, more profound and longer duration of neutropenia, increased use of long-dwelling intravenous catheters, use of antacids and histamine blockers, and use of prophylactic antibacterial agents with relatively weak coverage of gram-positive organisms (Kanamaru and Tatsumi, 2004).

This change in prevalence from gram-negative to gram-positive bacteria in bacteremia was also reported in previous studies conducted at several centers in Thailand between the years 2003 to 2009. The characteristics of FN episodes, such as gender, initial temperature, and initial ANC, were similar between those studies and the present study. There was also similarity between those studies and ours for the most common underlying diseases, which were ALL, acute non-lymphoblastic leukemia, lymphoma, and solid tumors, respectively (Sanpakit *et al*, 2005; Laoprasopwattana *et al*, 2007). The most common organism among patients with bacteremia was coagulase-negative *Staphylococcus* (*Staphylococcus aureus*), which is a common gram-positive organism often associated with indwelling central venous catheters. However, all FN episodes in our study that had coagulase-positive *Staphylococcus* bacteremia were not catheter-related.

Bacteremia was documented in only 5.6%

of FN episodes in this study. This might be one of the reasons for our low 0.93% mortality rate. This rate is on the low end of the mortality range reported in recent pediatric studies of FN that ranged from 0.7% to 3.9% (Rackoff *et al*, 1996; Klaassen *et al*, 2000; Baorto *et al*, 2001; Santolaya *et al*, 2001 Hodgson-Viden *et al*, 2005; Sanpakit *et al*, 2005). The incidence of microbiologically-confirmed infections was low, because not all body sites were accessible for culture sampling. Similarly, nasopharyngeal wash to investigate for respiratory virus was not performed in all cases of respiratory tract infection due to the fact that many patients could not afford the cost.

Decision-making regarding antibiotic therapy is critical in the initial management of FN patients, and there is significant variability across centers in the empiric antibiotic regimens used to treat FN. The goal of empiric antibiotic therapy is to cover the most commonly prevalent pathogens, such as gram-negative bacilli, including *Pseudomonas aeruginosa* and viridans group streptococci, in high-risk FN patients without definite source of infection (Downes *et al*, 2013).

No difference in treatment failure, mortality, or adverse effects was observed when antipseudomonal penicillins were compared with antipseudomonal cephalosporins or carbapenems (Manji *et al*, 2012). The overall response rate reported in a previous study was 62.2% (Sanpakit *et al*, 2005). Our initial treatment was based on this knowledge, and our overall response to initial treatment was 77.5%. However, use of antimicrobials that could cover gram-positive bacteria rarely in the cause of FN should be considered based on this shift of bacterial spectrum especially in patients with high-risk features to get gram-positive bacterial infection.

All death in our study occurred during relapse of acute leukemia. From our analysis, ANC on day 3 <100/mm^3 was found to be a significant predictor of both prolonged duration of fever and unresponsiveness to the first regimen of antibiotics. The use of prophylactic G-CSF in oncology patients remains controversial. If the risk of FN is high after intensive chemotherapy, G-CSF is recommended. A statistically significant correlation was observed between G-CSF usage and shorter duration of FN treatment in our study (p<0.01). However, previous studies reported little evidence that G-CSF could decrease the infection-related mortality rate, even if the duration of neutropenia was shortened (Sung *et al*, 2004; Smith *et al*, 2006). The decision to use or not use prophylactic G-CSF should be based on a cost/benefit analysis in each individual case.

This study has some mentionable limitations. First and consistent with the retrospective nature of this study, some patient data may have been missing or incomplete. Second, the size of the study population was relatively small. As a result, our study may have lacked sufficient power to identify all significant associations. Third, the patients enrolled in this study were from a single center. Fourth, our center is Thailand's largest tertiary referral hospital, which means that we often have referred patients with complicated and intransigent conditions. As such, it is possible that our findings may not be generalizable to patients with the same condition in other settings.

In conclusion, good response to treatment and low mortality was observed among the pediatric cancer patients with FN that were included in this study. Laboratory evaluation for viral pathogen, especially in patients with signs and symptoms of respiratory tract infection, should be strongly considered. A shift in tendency from gram-negative to gram-positive bacteria as the common pathogens in bacteremia is also emphasized.

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CONFLICTS OF INTEREST

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

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