Evaluation of Guideline for Treatment of Febrile Neutropenia in Pediatric Cancer at Siriraj Hospital

Kleebsabai Sanpakit MD*, Kamon Phuakpet MD*,
Gavivann Veerakul MD*, Nattee Narkbunnam MD*,
Kulkanya Chokephaibulkit MD

*Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Background: *Febrile neutropenia (FN) is a common and important clinical problem in pediatric cancer. Our Institution has developed a clinical practice guideline (CPG) for treatment of FN to assist the clinicians taking care of these patients.*
Objective: *To evaluate characteristics of FN, sources and causative agents of infection, applicability and effectiveness of the CPG, and factors that associated with response to treatment.*
Materials and methods: *The medical records of patients with FN that had completed data from September, 2003 to May, 2005 were reviewed and analysed.*
Results: *A total of 148 FN episodes in 90 patients were analysed. The predominant underlying malignancy was acute leukemia. About 50% had absolute neutrophil count (ANC) less than 100 cells/mm^3 at the beginning and at reassesment on day 3 of treatment. The causes of infection with microbiological confirmation was 25%. Urinary tract infection was the predominant source of infection and gram negative bacteria was the predominant causative agent. Sixty-two percents responded to initial treatment without changing of antibiotics. Of all episodes, 91.2% were able to complete treatment according to the CPG. The mortality rate was 1.4%. ANC of less than 100 cell/mm^3 on day 3 of treatment was the significant risk factor for prolonged duration of fever and unresponsiveness to low risk regimen of antibiotics. ANC of less than 100 cell/mm^3 on day 3, having hematologic malignancies, and recurrent fever were associated risks for the need for antifungal agent or referral to infectious diseases specialist or death. The pretreatment ANC more than 100 cells/mm^3 was a significant predictor for the responsiveness to low risk regimen without recurrent fever.*
Conclusion: *Our CPG could practically be applied in FN patients and resulted in low mortality rate.*

Key word: *Clinical Practice Guideline, Febrile neutropenia, Pediatric cancer*

J Med Assoc Thai 2005; 88(9): S124-34
Full text. e-Journal: *http://www.medassocthai.org/journal*

Febrile neutropenia (FN) is a common problem in pediatric oncology and is a medical emergency requir-ing prompt in-hospital evaluation and administration of broad-spectrum antibiotics[1-5]. Because approximate-ly 60% of FN episodes are caused by bacterial infections with or without bacteremia[4,6], and predisposes to overwhelming sepsis[7], the standard practice is to start empiric intravenous antibiotics if the absolute neu-trophil count (ANC) is below 500-1000 cells/mm^3 and add antifungal agents if fever persists[3,7,8]. Over the past several decades, there has been a substantial pro-gress in the management of patients with FN[9]. While diagnostic and therapeutic interventions have substantially improved during this period, increases in the num-ber of patients with FN, changes in the predominant pathogens and patterns of infection, and increases in antibiotics resistance have continued to be problematic[2,9-11].The empirical choice of antimicrobials should depend on the local predominant pathogens and resistance patterns. Prompt initiation of antimicrobial therapy remains the gold stan-

Correspondence to: Kleebsabai Sanpakit, MD, Hematology-Oncology Division, Department of Pediatrics Faculty of Medicine, Siriraj Hospital Mahidol University, Bangkok 10700 Thailand Tel: +662-4197000 Ext.5971, Fax: +662-8663021 E-mail: sisap@mahidol.ac.th

dard[9]. Since patients with FN represent a heterogeneous population with varying rates of infection-related morbidity and mortality, it is important to develop the risk-stratification models to identify the patients at low and high risk of serious complications in order to deliver the most appropriate management to individual patients[2,9, 11-14].

Our Institution has developed the clinical practice guideline (CPG) for FN since September 2003. The purpose of these guidelines is to assist clinicians on decision of the treatment and to avoid inappropriate use of antibiotics in patients with FN. The objective of this study were: 1) to evaluate this CPG, 2) to determine the characteristics of FN in our patient population, 3) to identify the sources and etiologic agents of infection, and 4) to evaluate the factors associated with response to the empirical treatment according to CPG.

Meterials and methods

A CPG for pediatric cancer patients with FN were prepared by a panel of experts in pediatric oncology and infectious diseases at Siriraj hospital. The guideline was based on the scientific publications, previous data of infections in pediatric patients with cancers and FN at Siriraj hospital, and peer-reviewed information.This guideline had been applied to patients with FN after or during on chemotherapy in Department of Pediatrics, Siriraj hospital since September, 2003. The final guideline was shown in Figure 1. Fever was defined as a single oral temperature of $\geq$ 38.3°c or a temperature of $\geq$ 38.0°c for $\geq$ 1 hour. Neutropenia was defined as an ANC < 500 cells/mm^3, or < 1000 cells/mm^3 with a predicted decrease to < 500 cells/mm^3 [8]. Febrile neutropenic patients were thoroughly examined and investigated in an attemp to identify source of infection. All patients were started on the 1st regimen except high risk patients whom were started on the 2nd regimen. The detail of treatment regimens were shown in the footnote of Figure 1. The medical record with completed data were retrospectively reviewed for demographic data, source of infection, response to initial antibiotic the-rapy, subsequent recurrent fever and ultimate outcome of treatment. A recurrent fever was defined as a new fever that occurred after the patient had been afebrile for $\geq$ 24 hours. If patient had recurrent fever during the treatment, this would not be counted as the new episode of FN.

The data was analysed by using SPSS for window (Chicago,IL). Descriptive statistics were used to summarize the clinical data and continuous variables which were expressed as frequency, percentage, mean, median, and standard deviation ($\pm$SD). Outcome results were compared between each variable factor by using chisquare test or Fisher's exact test, if required. We assessed the potential association of a number of covariates on response to the 1st regimen and outcome of treatment by using logistic regression analysis.

Results

A total of 148 episodes in 90 patients were analysed. The summary of demographic data and number of ANC were shown in Table 1. The sex were well balanced with 79.7% of episodes occurring in patients between 1-10 years old. The predominant cancer type was acute leukemia (71%) and 47.4% were in remission. Twenty seven percents occurred in relapsed or refractory cases. None of the patient had received a bone marrow transplantation. Profound neutropenia (ANC < 100 cells/mm^3) was found in 55.4% at the beginning and 52.8% at reassessment on day 3 of treatment. Fifty-five episodes (37.2%) had ANC on day 3 lower than day 1. The characteristics of FN episodes were shown in Table 2. The sources of infection were microbiologically confirmed at the onset of FN in 37 episodes (25%) (Table 3). The urinary tract infection was the predominant source and gram negative bacteria were the prominent pathogens. The age, initial temperature, number of ANC on day 1 and 3, duration of fever, and type of underlying malignancies were not different among the patients whose source of infection were able to be identified and those whose were not. Modified regimens were applied at the beginning or during the treatment in 37 episodes (25%, Table 4). Metronidazole was the most common modified antimicrobial agent.

Of the 148 episodes, three were defined as high risk because the patients had sign of sepsis and/or hypotension. Two of these had nonremission acute leukemia. The other had refractory rhabdomyosarcoma. Treatment in all 3 patients were started with the 2nd regimen consisted of imipenem and amikacin. The pathogen was identified in 2 patients. One of the these patients was found to have cholera. The other had tuberculous lymphadenitis. The rest of 145 FN episodes were started treatment with the 1st regimen, i.e., ceftazidime plus gentamicin in 143 episodes (98.6%), and piperacillin/tazobactam in 2 episodes. Ninety episodes (62.1%) responded without changing the antibiotics. Sixty-two of 148 episodes (41.9%) became afebrile on day 3. Ninety-two episodes (62.2%) responded to initial treatment regimen without changing antibiotics

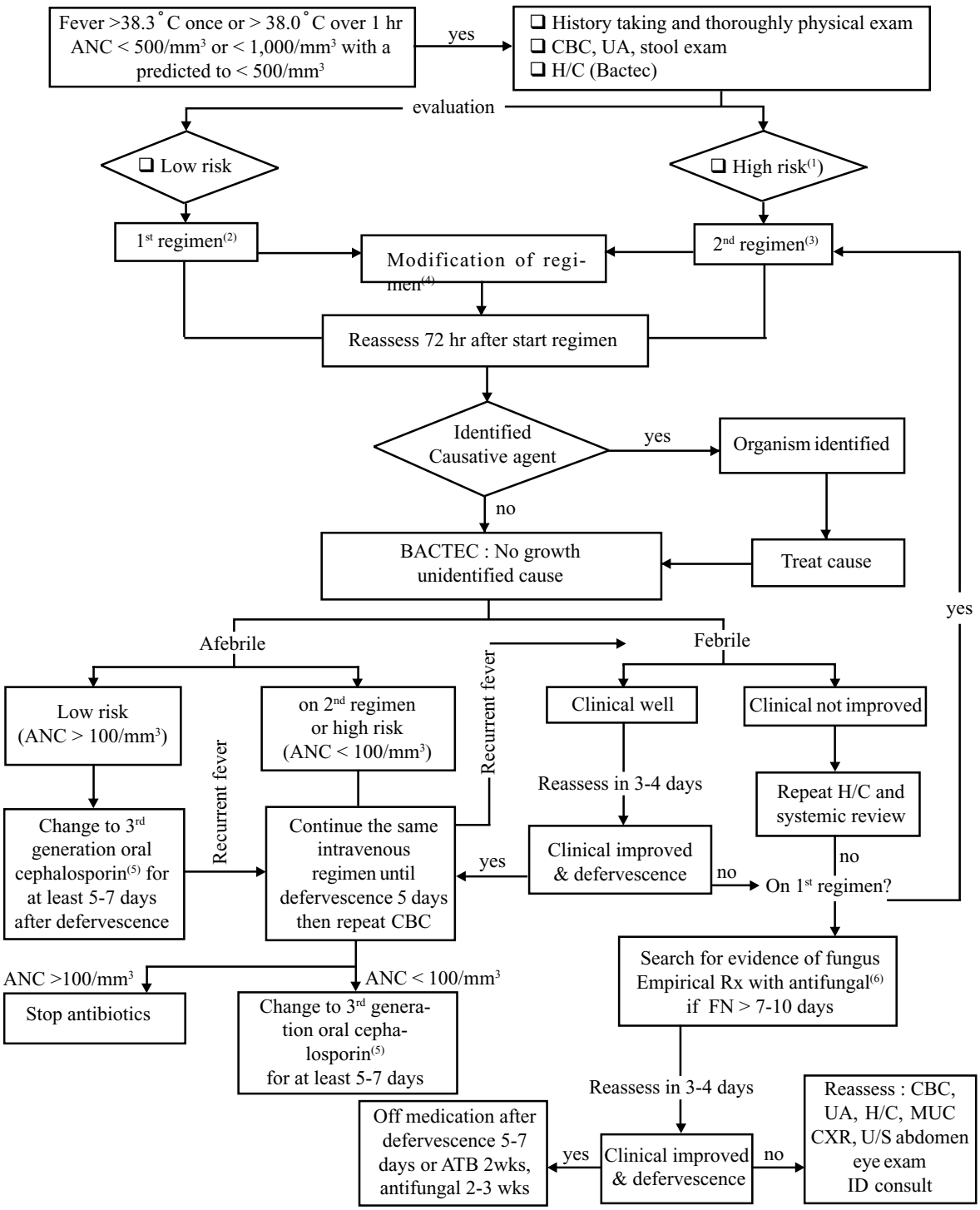

Fig. 1 Clinical Practice Guideline for Patients with Febrile Neutropenia

Abbreviation: CBC= complete blood count, UA= urine analysis, Rx= treatment, FN= febrile neutropenia, ATB= antibiotic, H/C= hemoculture, MUC= midstream urine culture, CXR= chest X-ray, U/S= ultrasound, ID= infectious disease

Figure 1. Clinical Practice Guideline for Patients with Febrile Neutropenia (continued)

Footnote:

(1) High risk : shock, hypotension, poor perfusion, acute respiratory distress syndrome, confuse, sign and symptom of sepsis, agitation

(2) 1st Regimen Antibiotics
2.1 Ceftazidime 100-150 mg/kg/day q 8 hr+ Gentamicin 5 mg/kg/day q 8 hr
2.2 Piperacillin/tazobactam (400-500 mg/kg/day q 6 hr) for patient with renal insufficiency
2.3 4th generation cephalosporin (cefepime 100 mg/kg/day q 12 hr) for patient with renal insufficiency

(3) 2nd Regimen Antibiotics
3.1 Imipenem 80-100 mg/kg/day+ Aminoglycoside (Amikacin or Netilmycin, if patient had renal insufficiency).
3.2 Meropenem for patient with underlying neurological disorder.

(4) Modification instruction (add on (2) or (3) if patient has indication)
4.1 Add cloxacillin if patient has sign of skin or soft tissue infection (e.g. abscess, cellulitis, thrombophlebitis).
4.2 Add vancomycin if patient has risk of MRSA or coagulase negative staphylococci infection (e.g. ventriculoperitoneal shunt, central line, history of previous colonization with MRSA within 1 year).
4.3 Add metronidazole if patient has risk of anaerobes infection (e.g. perianal abscess, typhlitis) and does not receive 2nd regimen.
4.4 Add acyclovir if patient has herpetic-like oral ulcer with positive Tzanck smear or fluorescence antibody staining.
4.5 Add metronidazole if patient has diarrhea especially in case whom pseudomembranous colitis can not be ruled out.
4.6 Add oral fluconazole 3-5 mg/kg/day OD if patient has oral thrush.
4.7 Add penicillin if patient has severe mucositis and does not receive piperacillin/ tazobactam or 2nd regimen.
4.8 If patient has tachypnea, hypoxia and diffuse bilateral infiltration in CXR, investigation for pneumocystis carinii and empirical treatment with Co-trimoxazole 20 mg/kg/day should be initiated.

(5) Oral 3rd generation cephalosporin for step down therapy
5.1 Ceftibuten 9 mg/kg/day OD.
5.2 Cefixime 8 mg/kg/day OD.
5.3 Cefpodoxime 10 mg/kg/day OD or BID.
5.4 Cefdinir 14 mg/kg/day OD or BID.

(6) Antifungal treatment for systemic infection
6.1 Amphotericin B test dose 1 mg, if no reaction start with dose 0.25 mg/kg then increase to 0.5 mg/kg and 1 mg/kg every 12-24 hours depend on clinical severity. In severe case, amphotericin B can be started at 0.5 mg/kg after test dose and increase dose to 1 mg/kg in 24 hours then maintenance dose at 1 mg/kg/day
6.2 Patient who has severe reaction with amphotericin B even after premeditation, intravenous fluconazole can be started. Pediatric infectious clinicians should be informed and consulted.

Abbreviation: MRSA= methicillin-resistant *Staphylococcus aureus*

or need for antifungal agents. Twenty-two episodes (14.9%) had recurrent fever during the treatment and were treated according to the CPG; all had resolution of fever. Antibiotics was switched to oral form before discontinuation of treatment in 44 episodes (29.7%). Granulocyte colony stimulating factor (G-CSF) were applied in 11 episodes (7.4%) with profound or protracted neutropenia with severely ill condition. Twenty-five episodes (16.9%) required amphotericin B but none had documented fungemia. Six of these did not response and needed to be referred to infectious diseases specialists.

Two patients (1.4%) died during the treatment (Fig.2). Both had acute leukemia in nonremission state. One was started treatment with high risk regimen due to clinical sign of sepsis and died on day 2 of the treatment. The other was treated with low risk regimen and was changed to high risk regimen later on due to unresponsiveness. She developed septic shock and died on day 17. All cultures in both patients were negative.

Table 1. The demographic data and number of ANC

Factors	Frequency	Percentage (%)
1. Sex : male/female	73 /75	49.3 /50.7
2. Age (year)		
< 1	4	2.7
1-4.9	53	35.8
5-9.9	65	43.9
>10	26	17.6
3. Diagnosis		
- Hematologic malignancy		
ALL	59	39.9
ANLL	46	31.1
Large cell lymphoma	7	4.7
Burkitt s lymphoma	2	1.4
- Non-Hematologic malignancy		
Solid tumor		
Neuroblastoma	7	4.7
Rhabdomyosarcoma	6	4.1
Hepatoblastoma	5	3.4
Osteosarcoma	3	2.0
Pleuropulmonary blastoma	3	2.0
Medulloblastoma	3	2.0
CNS GCT	2	1.4
Peripheral nerve sheath tumor	2	1.4
Wilm's tumor	1	0.7
Ewing sarcoma	1	0.7
LCH	1	0.7
4. Stage of hematologic malignancy (N=114)		
Remission	54	47.4
Nonremission	60	52.6
5. Severity of disease		
Nonrelapsed cases	108	73.0
Relapsed/Refractory cases	40	27.0
6. ANC at the beginning of treatment (cell/mm^3)		
< 100	82	55.4
100-199	23	15.5
200-499	34	23.0
> 500	9	6.1
7. ANC on day 3 of treatment (cell/mm^3)		
< 100	78	52.8
100-199	20	13.5
200-499	31	20.9
> 500	19	12.8

Abbreviation: ALL= acute lymphoblastic leukemia, ANLL= acute nonlymphoblastic leukemia
CNS GCT= central nervous system germ cell tumor, LCH= Langerhan cell histiocytosis, ANC= absolute neutrophil count

Table 2. The characteristics of febrile neutropenia episodes

Factors	Mean ± SD	Median	Range
Age (year)	6.76 ± 3.73	5.55	0.4 - 15.7
initial temperature (°c)	39.04 ± 0.56	39.00	38.0 - 40.9
ANC on Day 1 (cell/mm^3)	148.09 ± 189.01	60	0 - 800
ANC on Day 3 (cell/mm^3)	251.57 ± 438.46	91	0 - 2744
Duration of fever (day)	4.81 ± 4.45	3	1 - 24

Table 3. Sources of infection and causative agents

source of infection	Frequency	Percent
1. Sources of infection		
Unidentify	111	75.0
Urinary tract infection	13	8.8
Oral thrush	7	4.7
Sepsis	6	4.1
Mucositis	5	3.4
Gastroenteritis	2	1.4
Upper Respiratory Tract	2	1.4
Pneumonia	1	0.7
Lymphadenitis	1	4.7
2. Causative agents		
2.1 Unidentified	111	75.0
2.2 Gram negative bacteria		
Nonfermentative gram negative rod	9	6.1
E.coli	6	4.1
Vibrio cholera	1	0.7
Proteus mirabilis	1	0.7
Salmonella group E	1	0.7
Pseudomonas aeruginosa	1	0.7
2.3 Gram positive bacteria		
Coagulase negative staphyllococcus	2	1.4
2.4 Viral		
Herpes simplex virus	5	3.4
Respiratory virus	2	1.4
2.5 Candida	7	4.7
2.6 Tuberculosis (TB)	1	0.7
2.7 *Mycoplasma pneumoniae*	1	0.7

Patients with underlying hematologic malignancies tended to have longer duration of fever than those with other malignancies (mean±SD; 5.1±4.8 vs 3.8±2.9 days respectively, p value=0.055). The characteristics of FN, i.e. the initial temperature, the ANC on day 1 and day 3, the chance to identify source of infec-tion, and to have recurrent fever; were not statistically different between the patients with hematologic versus nonhematologic malignancies or between the patients with remission hematologic malignancy versus in nonremission, respectively.

Table 4. Modified regimens

modification regimens	Frequency	Percent
none	111	75.0
cloxacillin	2	1.4
vancomycin	1	0.7
acyclovir	6	4.1
metronidazole	12	8.1
fluconazole	8	5.4
penicillin	2	1.4
metronidazole & acyclovir	1	0.7
metronidazole & fluconazole	2	1.4
fluconazole & penicillin	1	0.7
metronidazole, fluconazole & vancomycin	1	0.7
metronidazole, acyclovir, vancomycin & penicillin	1	0.7

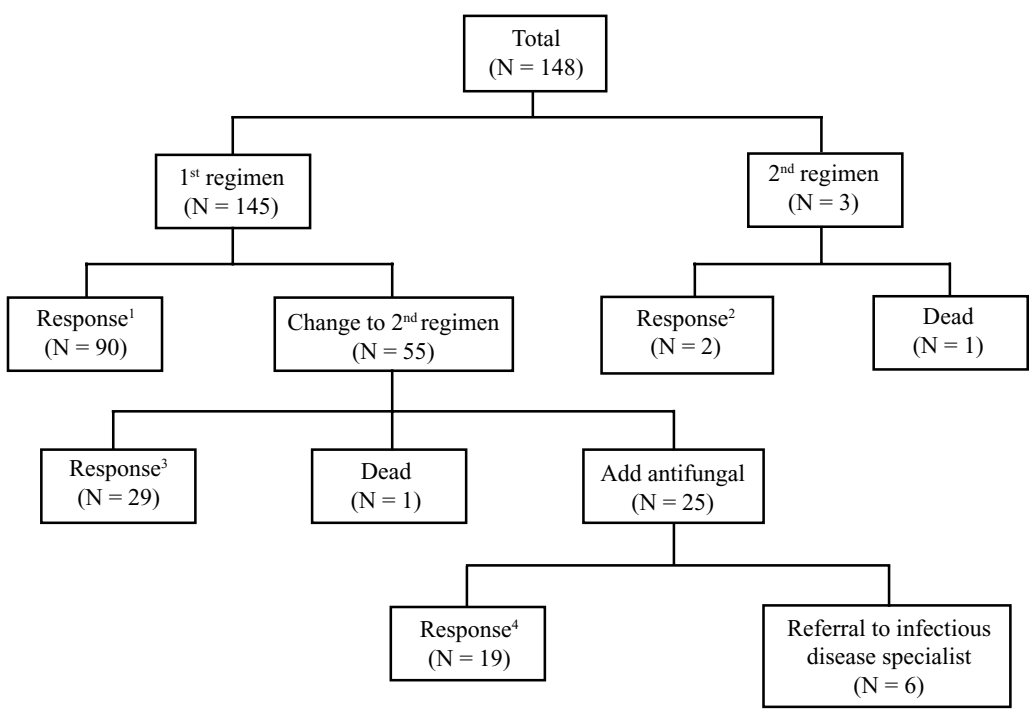

Fig. 2 Summary of febrile neutropenia episodes

Footnote : mean duration of fever; 1 = 2.9 $\pm$ 2.4 days (1-18 days), 2 = 3.0 $\pm$ 2.8 days (1-5 days), 3 = 7.6 $\pm$ 4.6 days (4-24 days), 4 = 10.8 $\pm$ 3.3 days (4-18 days)

One hundred and thirty five episodes (91.2%) were able to complete treatment following the CPG. Thirteen episodes did not follow the CPG. Most of the deviation from CPG was that the intravenous antibiotics were not switched to oral form. Five episodes of FN (3.4%) had recurrent of fever within 7 days after

discontinuation of antibiotics. Three of them were newly diagnosed acute leukemia during induction phase. The others were refractory rhabdomyosarcoma and refractory acute myeloid leukemia, consecutively. All of them were started treatment of previous FN episodes with the 1st regimen and two were changed to the 2nd regimen before the end of treatment. All of these recurrent episodes were counted as new FN and were restarted treatment according to risk stratification of the CPG.

The patients who had ANC on day 3 < 100 cells/mm^3 had significantly longer duration of fever than those with ANC day 3 > 100 cells/mm^3 (mean$\pm$SD = 5.66 $\pm$ 5.21 vs 3.86 $\pm$ 3.18 days, *p* value=0.012). The FN episodes which occurred in hematologic malignancy patients had tendency to be longer than in nonhema-tologic malignancy (mean$\pm$SD = 5.12 $\pm$ 4.79 vs 3.79 $\pm$ 2.89 days, *p* value=0.052). The ANC at the time of reas-sessment (day 3) was significantly higher in the group that responded to the 1st regimen (mean$\pm$SD = 341.07$\pm$526.77 vs 97.54$\pm$152.52 cells/mm^3, *p* value = 0.000). However, the ANC on day 1, age group, and initial temperature were not associated with response to 1st regimen. The patients with ANC on day 3 < 100 cells/mm^3, or had recurrent fever responded significantly poorer and needed to change antibiotic to the 2nd regimen (OR 2.22; *P* value=0.019 and OR 6.88; *p* value=0.001 respectively). The patients with ANC on day 1 < 100 cells/mm^3 also had higher tendency to be unresponsive to the 1st regimen (OR 1.98; *p* value = 0.051). Having hematologic malignancy, being relapsed/refractory diseases, or discovery of pathogen was not significantly associated to the unresponsiveness to the 1st regimen or prolonged duration of fever.

From 148 episodes of FN, 48 (32.4%) had good response to the initial antibiotics and became afebrile on day 3 without recurrent fever during or within 7 days after discontinuation of the treatment. Multivariate analysis with logistic regression found that only ANC > 100 cells/mm^3 on day 1 was associated with good response (42% vs 18%, *p* value=0.01). These patients had significantly higher ANC on day 1(mean 194.2$\pm$204.3 cells/mm^3) than the rest (mean 125.95$\pm$178.04 cells/mm^3, *p* value=0.039). Patients who needed antifungal treatment or referral to the infectious diseases specialist or died, classified as poor response group, were found in 28 episodes (18.9%) in this study. These patients had significantly lower ANC on day 3 compare to the rest (mean 96.8$\pm$153.0/mm^3 vs 285.6$\pm$473.6/mm^3, *p* value=0.000). The patients with ANC on day 3 < 100 cells/mm^3, with underlying hematologic malignancies, or with recurrent fever, had significantly higher chance to have poor response (OR 2.67; *p* value=0.028, OR 10.24; *p* value=0.007, OR 3.18; *p* value=0.024, respectively). However, the ANC on day 1 < 100 cells/mm^3 was not a significantly predictor for poor response. Having hematologic malignancies, being relapsed/refractory diseases, and identifiable sources of infection were not predictor for either good or poor response.

Discussion

It has been reported that FN occurred in 10-50% of patients with solid tumors and in more than 80% of those with hematologic malignancies[12]. In our study, FN occurred 3.5 time more often in hematologic malignancies than in solid tumors. This could be from more aggressive and longer and continuing duration of treatment in hematologic malignancies compare a to intensive pulse treatment in solid tumors. Moreover the bone marrow reserve in hematologic malignancies is usually affected by the underlying disease especially in those who were not in remission. All of these made hematologic malignancies more prone to develop FN. Previous studies concluded that children with cancer could be separated into different risk categories according to clinical and laboratory parameters presented at the time of FN. Patients with hematologic malignancies and recipients of bone marrow transplantation were at higher risk than those with solid tumors because the duration of severe neutropenia often exceeded 15 days. In contrast, most patients with solid tumors had neutropenia lasting $\leq$ 7-10 days.

The most common modified regimen that was used in our patients was metronidazole since diarrhea was the common symptom that occurred during FN episodes. It was reported that majority of patients with FN did not have a microbiologically confirmed infection, but those who did were at risk for overwhelming sep-sis[7]. Historically, sources of infection were identified in 25-50% of FN patients and additional 12-25% were found to have bacteremia especially in patients with ANC < 100 cells/mm^3 [4,8,15-17]. One recent study of 275 FN episodes showed microbiologically confirmed infections in 21%; 75% of which were attributed to bacterial infections and 25% were viral infections. Bacteremia was documented in 12% of FN episodes[7]. These were comparable to the findings in our study. We found microbiologically confirmed infections in 25%; 56.8% of which were attributed to bacterial infection which mainly involved the urinary tract system and 18.9% were viral infection. Bacteremia was docu-

mented in only 4.1% of FN episodes in our study. This might be one of the reason for our low mortality rate. The incidence of microbiologically confirmed infections might be low because not all body sites were accessible for sampling for culture, and some infections could be from cell-wall deficient organisms which were not detected in routine cultures[7,18]. In the past three decades, aerobic gram-negative bacilli were the predo-minant organisms with *Pseudomonas aeruginosa* as a leading isolate[2]. The presence of gram-negative rod bacteremia is associated with high mortality rates. These facts led to the administration of a combination of a β-lactam with antipseudomonas activity and an aminoglycoside as the empirical treatment, which resulted in an overall response rate of 60-70%[9].

Our initial treatment was based on these knowledge and overall response to initial treatment were comparable (62.2%). Recently, the spectrum of bacterial causing infection began to change in Western countries with a steady increase in gram-positive pathogens. In the United States, 60-70 % of bacteremia with a single organism identified were caused by gram-positive cocci mainly *coagulase-negative Staphylococci, Enterococci* and *S.aureus*[2,8,10,14,19,20]. The cause of this change had not been clearly identified and was probably multifactorial included a aggressive chemotherapeutic regi-mens that caused 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 anti-bacterial agents with relatively weak coverage of gram-positive organisms[2,10,19,20]. Invasive fungal infections tend to occur later in the course of neutropenia than do bacterial infections. The herpes viruses and community acquired respiratory viruses had emerged as important pathogens in selected subsets of patients and some had a seasonal distribution[1,10,14,21]. Our data revealed gram-negative bacteria to still be the predominant caused of infections. This was probably due to the fact that few of our patients had long-indwelling intravenous catheters; and the histamine blocker was not widely used. Moreover, the most common site of infection in our FN episodes was urinary tract system in which gram-negative organism was frequently isolated.

The adjunctive use of G-CSF could reduce the risk, severity, and duration of FN which resulted in reducing the amount of time spent in hospital[16,22,23]. Despite these benefits, G-CSF were not recommended to administer in all FN patients because of its high costs. The selective use of G-CSF in only patients at greater risk for neutropenic complication might increase its cost-effectiveness[23]. Only 7.4% of our patients received G-CSF. The number was too small to analyse the significant benefit from its use.

The applicability of our CPG was achievable considering that 91.2% of FN episodes were able to complete treatment following the CPG. The optimal duration of antibiotic treatment in FN was crucial to avoid recurrence of a partially treated bacterial infection. In our study, the recurrent rate of fever within 7 days after discontinuation of antibiotic was only 3.4%. All of these had underlying nonremission leukemia or refractory solid tumor which could contribute to recurrent fever. This also confirmed the appropriate duration of treatment in this CPG.

The magnitude of neutropenia was shown to correlate with a greater risk of infectious complications; especially when ANC < 100 cells/mm^3. Additional significant risk factors were also reported, such as age < 1 year, peak temperature ≥39^{o}c, presence of concurrent comorbidities, status and severity of the underlying malignancy (relapsed leukemia or refractory solid tumors)[4,7,23-26]. In this study, only 3 episodes were of high risk and all of these patients had active underlying diseases. Although majority of our patients had under-lying hematologic malignancies in nonremission state and one half had profound neutropenia at the beginning of treatment and at the reassessment on day 3, the overall mortality rate was only 1.4%; a figure which is lower than the previous reports of almost 10% mortality rate[12,13]. All death in our study occurred during nonre-mission state of acute leukemia which could be one factor that attributed to the mortality.

From the analysis, we found that an ANC on day 3 < 100 cells/mm^3 was a significant predictor of prolonged duration of fever and unresponsiveness to the 1st regimen of antibiotics. We found ANC on day 3 lowered than in day 1 in a significant number of FN episodes (37.2%). Moreover, an ANC on day 3 < 100 cells/mm^3, as well as, the underlying hematologic malignancies and recurrence of fever during the treatment were also a significant predictor for the need of antifungus or referral to infectious disease specialist or dead. For those who responded to the initial treatment and became afebrile on day 3 without recurrent fever, an ANC on day 1 > 100 cells/mm^3 was a significant predictor. This point out the importance of ANC on both day 1 and day 3 for predicting the good or poor response.

Conclusion

The CPG developed by our institution could be practically applied in pediatric oncology patients with low mortality rate. The overall response of the treatment was satisfactory. Further study for very low risk patients that may be treated as outpatient setting is warranted.

References

1. Pizzo PA. Fever in immunocompromised patients. N Engl J Med 1999;341:893-900.
2. Donowitz GR. Infections in the neutropenic patient: an overview. In: Schechter GP, Broudy VC, Williams ME, eds. Hematology 2001 American Society of Hematology Educational program book. Washington : Amgen Oncology, 2001: 113-8.
3. Bodey GP, Bruckley M, Sathe YS, Freireich EJ. Quantitation relationships between circulating leukocytes and infection in patients with acute leuke-mia. Ann Int Med 1996;64:328-40.
4. Santolaya ME, Alwarez AM, Becker A, et al. Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia and fever. J Clin Oncol 2001;19:3415-21.
5. Pizzo PA, Rubin M, Freifeld A, Pizzo PA, Rubin M, Freifeld A, Walsh TJ. the child with cancer and infection: Empiric therapy for fever and neutropenia and preventive strategies. J Pediatr 1991;119:679-94.
6. Klastersky J. Febrile neutropenia. Curr Opin Oncol 1993;5:625-32.
7. Hodgson-Viden H, Grundy PE, Robinson JL. Early discontinuation of intravenous antimicrobial therapy in pediatric oncology patients with febrile neutropenia. BMC Pediatrics 2005;5:10-6.
8. Hughes WT, Armstrong D, Bodey GP, Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, Pizzo PA, Rolston KV, Shenep JL, Young LS. 2002 guidelines for use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34:730-51.
9. Sipsas NV, Bodey GP, Kontoyiannis DP. Perspectives for the management of febrile neutropenic patients with cancer in the 21st century. Cancer 2005; 103:1103-13.
10. Picazo JJ. Management of the febrile neutropenic patients: a consensus conference. Clin Infect Dis 2004;39:S1-6.
11. Bodey GP. Managing infections in the immunocompromised patient. Clin Infect Dis 2005;40: S239.
12. Klastersky J. Management of fever in neutropenic patients with different risks of complications. Clin Infect Dis 2004;39:S32-7.
13. Elting LS, Rubenstein EB, Rolston K, Elting LS, Rubenstein EB, Rolston K, Cantor SB, Martin CG, Kurtin D, Rodriguez S, Lam T, Kanesan K, Bodey G. Time to clinical response: an outcome of antibiotic therapy of febrile neutropenia with implications for quality and cost of care. J Clin Oncol 2000;18:3699-706.
14. Rolston KVI. The infectious diseases society of Americe 2002 guidelines for the use of antimicrobial agents in patients with cancer and neutropenia : Salient features and comments. Clin Infect Dis 2004;39:S44-8.
15. Kern WV, Cometta A, Bock RD, Kern WV, Cometta A, De Bock R, Langenaeken J, Paesmans M, Gaya H. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. N Eng J Med 1999;341:312-8.
16. Perrone J, Hollander JE, Datner EM. Emergency department evaluation of patients with fever and chemotherapy induced neutropenia. J Emerg Med 2004;27:115-9.
17. Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 1993;328:1323-32.
18. Woo PC, Wong SS, Lum PN, Hui W, Yuen K. Cell-wall-deficient bacteria and culture-negative febrile episodes in bone-marrow-transplant recipients. Lancet 2001;357:675-9.
19. Giamarellou H, Antoniadou A. Infectious complications of febrile leukopenia. Infect Dis Clin North Am 2001;15:457-82.
20. Kanamaru A, Tatsumi Y. Microbiological data from patients with febrile neutropenia. Clin Infect Dis 2004;39:S7-10.
21. Whimbey E, Englund JA, Couch RB. Community respiratory virus infections in immunocompromised patients with cancer. Am J Med 1997; 102:10-8.
22. Clark OAC, Lyman GH, Castro AA, Clark LGO, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. J Clin Oncol 2005;23:4198-214.
23. Lyman GH, Lyman CH, Agboola O, for the ANC study group. Risk models for predicting chemothe-

rapy-induced neutropenia. Oncologist 2005;10: 427-37.
24. Rolston KVI, Rubenstein EB, Freifeld A. Early empiric antibiotic therapy for febrile neutropenia patients at low risk. Infect Dis Clin North Am 1996; 10:223-37.
25. Yoshida M, Ohno R. Antimicrobial prophylaxis in febrile neutropenia. Clin Infect Dis 2004; 39:S65-7.
26. Peralta GS, Salzman CT, Garcia GJJ, Aquado EJ, Giralt GA, Cubells LC. Bacteremia risk criteria in the predictic febrile neutropenic cancer patient. Clin Transl Oncol 2005;7:165-8.

การวิเคราะห์แนวทางปฏิบัติในการรักษาภาวะไข้และเม็ดเลือดขาวต่ำในผู้ป่วยเด็กโรคมะเร็ง โรงพยาบาลศิริราช

กลิบสไบ สรรพกิจ, กมล เผือกเพ็ชร, กวิวัณณ์ วีรกุล, นัทธี นาคบุญนำ, กุลกัญญา โชคไพบูลย์กิจ

บทนำ: *ภาวะไข้และเม็ดเลือดขาวต่ำเป็นปัญหาที่สำคัญและพบบ่อยในผู้ป่วยเด็กโรคมะเร็ง ภาควิชากุมารเวชศาสตร์ โรงพยาบาลศิริราช ได้จัดทำแนวทางปฏิบัติในการรักษาผู้ป่วยกลุ่มนี้เพื่อช่วยแพทย์ในการดูแลรักษาผู้ป่วยให้มีประสิทธิภาพมากที่สุด*

วัตถุประสงค์: *เพื่อที่จะศึกษาลักษณะของภาวะไข้และเม็ดเลือดขาวต่ำ สาเหตุของไข้และเชื้อก่อโรคที่พบบ่อยในผู้ป่วยเด็กโรคมะเร็ง ประเมินผลในการนำแนวทางปฏิบัติในการรักษาไปใช้ในผู้ป่วยกลุ่มนี้ รวมทั้งวิเคราะห์หาปัจจัยที่มีผลต่อการตอบสนองต่อการรักษา*

วัสดุและวิธีการ: *เวชระเบียนผู้ป่วยเด็กโรคมะเร็งที่มีภาวะไข้และเม็ดเลือดขาวต่ำและมีข้อมูลครบถ้วนตั้งแต่เดือนกันยายน พ.ศ. 2546 ถึงเดือนพฤษภาคม พ.ศ. 2548 ได้ถูกนำมาเก็บข้อมูลและวิเคราะห์โดยวิธีการทางสถิติ ผลการศึกษาภาวะไข้และเม็ดเลือดขาวต่ำ 148 ครั้งในผู้ป่วย 90 รายได้รับการวิเคราะห์และพบว่าภาวะนี้พบได้บ่อยที่สุดในผู้ป่วยโรคมะเร็งเม็ดเลือดขาวเฉียบพลัน ผู้ป่วยถึงประมาณร้อยละ 50 มีปริมาณเม็ดเลือดขาวชนิดนิวโทรฟิลต่ำกว่า 100 เซลล์/ลบ.มม. เมื่อเริ่มต้นการรักษาและวันที่ 3 เมื่อมีการประเมินการรักษา ร้อยละ 25 พบสาเหตุของการติดเชื้อที่ได้รับการยืนยันจากผลการเพาะเชื้อ โดยตรวจพบเชื้อแบคทีเรียชนิดกรัมลบบ่อยที่สุด ส่วนสาเหตุของการติดเชื้อที่พบมากที่สุดคือ การติดเชื้อในระบบทางเดินปัสสาวะ ร้อยละ 62.2 ของผู้ป่วยทั้งหมดตอบสนองต่อการรักษาโดยไม่ต้องเปลี่ยนยาปฏิชีวนะ ร้อยละ 91.2 ได้รับการรักษาตามแนวทางปฏิบัติจนจบการรักษาโดยมีอัตราการเสียชีวิตเพียงร้อยละ 1.4 ปริมาณเม็ดเลือดขาวชนิดนิวโทรฟิลที่ต่ำกว่า 100 เซลล์/ลบ.มม.ในวันที่ 3 หลังเริ่มการรักษาเป็นปัจจัยที่มีผลต่อการตอบสนองต่อการรักษาที่ไม่ดีทำให้ผู้ป่วยมีไข้นานขึ้น และมีแนวโน้มต้องเปลี่ยนยาปฏิชีวนะจากกลุ่มที่มีความเสี่ยงต่ำเป็นกลุ่มที่มีความเสี่ยงสูง รวมทั้งยังสัมพันธ์กับผลการรักษาที่ไม่ดีโดยต้องเพิ่มการใช้ยาต้านเชื้อราหรือมีการปรึกษาหน่วยโรคติดเชื้อร่วมด้วยหรือมีโอกาสเสียชีวิตอย่างมีนัยสำคัญทางสถิต นอกจากนี้ผู้ป่วยที่เป็นโรคมะเร็งในระบบเลือดและต่อมน้ำเหลืองและผู้ป่วยที่มีการกลับมาเป็นซ้ำของไข พบว่ามีแนวโน้มที่จะมีผลการรักษาที่ไม่ดีอย่างมีนัยสำคัญทางสถิติ ส่วนผู้ป่วยกลุ่มที่มีผลการรักษาที่ดีมาก คือ ผู้ป่วยที่ไม่ต้องเปลี่ยนยาปฏิชีวนะและไม่มีการกลับเป็นซ้ำของไข้ พบว่ามีความสัมพันธ์ กับปริมาณเม็ดเลือดขาวชนิดนิวโทรฟิลเมื่อเริ่มการรักษาสูงกว่าหรือเท่ากับ 100 เซลล์/ลบ.มม. อย่างมีนัยสำคัญทางสถิติ*

สรุป: *แนวทางปฏิบัติในการรักษาภาวะไข้และเม็ดเลือดขาวต่ำในผู้ป่วยเด็กโรคมะเร็ง ซึ่งจัดทำโดยภาควิชากุมารเวชศาสตร์ โรงพยาบาลศิริราช สามารถนำไปใช้ได้ผลดีโดยมีอัตราการเสียชีวิตที่ต่ำ*