

Bacteremia in oncologic pediatric patients with febrile neutropenia at Chiang Mai University Hospital between 2007 and 2009

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Objectives To identify causative organisms and the antimicrobial susceptibility pattern in oncologic pediatric patients with febrile neutropenia (FN).

Methods A retrospective study in oncologic patients aged less than 18 years, who were admitted to the oncologic ward of the Department of Pediatrics, Chiang Mai University Hospital and diagnosed FN between January 2007 and December 2009.

Results One hundred and forty six patients with 305 episodes of FN were included in this study. The most common underlying disease of the patients was acute lymphoblastic leukemia (45.6%). Only 30 episodes had positive hemoculture. Gram negative bacteria were the pathogens (86.7%) isolated most frequently. Three of the most common causative organisms were *Acinetobacter baumannii* (27.6%), *Pseudomonas aeruginosa* (16.7%) and *Escherichia coli* (10%), consecutively. Eighty eight percent of *A. baumannii* specimens were sensitive to colistin, but only 37.5% to piperacillin/tazobactam, ceftazidime and amikacin. *P. aeruginosa* and other Gram negative bacteria were still 100% sensitive to ceftazidime and amikacin, except for the extended spectrum of beta-lactamase bacteria and *Stenotrophomonas maltophilia*. The cure rate of treatment within the current guideline was 94.1%. However, the outcome of patients with *A. baumannii* septicemia was as high as 50% (4 of 8 patients).

Conclusion *A. baumannii* is an emerging organism of FN among pediatric patients with malignancies in Chiang Mai University Hospital. Although the current FN guideline is still effective, carbapemen and colistin should be given early in pediatric FN patients who are at risk of *A. baumannii* bacteremia in order to reduce the mortality rate from this organism. **Chiang Mai Medical Journal 2012;51(3):71-78.**

Keywords: febrile neutropenia, children, oncologic, bacteremia, *Acinetobacter baumannii*

Introduction

Febrile neutropenia (FN) is an important cause of death among oncologic pediatric patients. It is defined by those who have a fever of more than 38.3 °C at one time or more than 38 °C twice

within 1 hour; plus an absolute neutrophil count (ANC) of less than 500 cells/mm³ or ANC of less than 1,000 cells/mm³, with a tendency to decrease in number [1, 2]. Malignancies alone and bone marrow suppression from chemotherapy usually cause neutropenia in these patients, and this increases the risk of severe infection such as sepsis and severe pneumonia. Early recognition and immediate treatment can reduce the morbidity and mortality rate. However, causative organisms could not be identified in more than 50% of these patients. Therefore, empirical antibiotic therapy, based on the incidence of causative organisms in each individual institute, should be started and continued until culture results or any clinical changes are revealed.

Gram-negative (GN) bacteria, *Pseudomonas aeruginosa* (*P. aeruginosa*), *Escherichia coli* (*E. coli*) and *Klebsiella spp.*, were the most common organisms found in patients with FN, and this was reported in many countries and in Thailand [3-6], and from our institution [7]. According to previous studies, monotherapy and a combination of antibiotics, which can cover these organisms, could be used as empirical antibiotics against GN bacterial infection.

Gram-positive (GP) bacteria, such as *Streptococcus viridans* and *Staphylococcus spp.*, are emerging organisms that have been found increasingly in western countries [8-10]. Wisplinghoff H, et al reported that the rate of GP infected patients with malignancies in the United States had increased from 62% in 1995 to 76% in 2000 [10]. Chanchalad P also reported an increase in GP bacteremia of up to 25.7% in oncologic pediatric patients at Maharat Nakhonratchasima Hospital, Thailand, between 2003 and 2007 [11]. However, Mecom J et al reported that the rate of GP bacteremia was only 17% in oncologic pediatric patients, at our institution, which was much less than GN bacteremia (83%) [7].

Ceftazidime and aminoglycosides are the first-line empirical antibiotics used in oncologic pediatric patients in institution, as they cover three of the most common organisms, including *P.*

aeruginosa, *E. coli* and *Enterobacter spp.*, which is in accordance with the study by Mecom J et al [7]. The efficacy of these empirical antibiotics is as high as 85-90%. If patients have severe clinical manifestations or do not respond to first-line treatment, meropenem and amphotericin would be replacements. However, these drugs are not so capable in treating some types of GP infection, especially *Staphylococcus spp.* Therefore, this study was carried out to identify the causative organisms in oncologic pediatric patients with FN. It also aimed to study the antimicrobial susceptibility pattern in order to evaluate the efficacy of the current treatment guideline, and improve the outcome of therapy, for reducing the morbidity and mortality rate in these patients.

Methods

This was a retrospective study in pediatric oncologic patients aged less than 18 years. All patients were diagnosed FN and admitted to the Oncologic Ward, Department of Pediatrics, Chiang Mai University (CMU) Hospital from 1st January 2007 to 31st December 2009. Their medical records were reviewed in order to gather demographic and clinical data, associated factors of infections, laboratory investigations, including hemoculture and antimicrobial susceptibility pattern, use of antibiotics, and outcomes. The outcome in this study was the mortality rate of patients with bacteremia and the cure rate was defined to percentage of patients who survived and had negative hemoculture after starting antibiotics.

Bacteremia was defined as a positive blood culture for at least one specimen, except for the diagnosis of coagulase-negative *Staphylococci* bacteremia that required a positive blood culture for 2 specimens. Hospital acquired infection was ascertained by that occurring 48 hours after admission, while community acquired infection was determined if patients had fever within the first 48 hours of admission, and at least 2 weeks from the previous admission.

This study was performed under the Helsinki Declaration of the World Medical Association and approved by the Ethic Committee of Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

Statistical analysis

All data were analyzed by the SPSS program version 17. Descriptive studies, including mean, median, standard deviation, ranges, frequencies and percentages were used to summarize clinical data. The Chi-square and Fisher's exact test were utilized to compare categorical data. Statistical sig-

nificance was accepted for a p-value of less than 0.05.

Results

One hundred and forty six patients which had 305 episodes of FN were included in this study. The demographic data are shown in Table 1. Three of the most common underlying diseases were acute lymphoblastic leukemia (ALL; 45.6%), acute non-lymphoblastic leukemia (ANLL; 20.3%) and solid tumors (19.3%), consecutively. Only 30 episodes (10%) had a positive hemoculture, and all except one were hospital acquired. Approximately half of the patients (45.7%) did not have specific symptoms of infection. Symptoms of upper respiratory tract infection (27.2%), gastrointestinal infection (13.8%) and skin lesions (7.9%) were the three found most commonly in these patients, as shown in Table 2. Only one patient had hypotension during the FN episode. The median white blood count (WBC) and ANC of these patients was 3,903.7 and 218.4 cells/mm³, respectively (Table 1).

GN bacteria were the pathogens isolated most frequently (86.7%), followed by GP bacteria (6.7%) and fungi (6.7%). Three of the most common causative organisms were *A. baumannii* (27.6%), *P. aeruginosa* (16.7%) and *E. coli* (10%). Two of the positive specimens for GP bacteria were identified as *S. viridans* and *Staphylococcus aureus*. One patient with hospital acquired infection was infected by *E. coli*. Intensive care unit (ICU) admission, central venous catheterization, and nasogastric and endotracheal intubation were the risk factors of GN and *A. baumannii* bacteremia, as shown in Table 3.

Eighty eight percent of *A. baumannii* specimens were sensitive to colistin and 50% to gentamicin and cefoperazone/sulbactam, but sensitivity to piperacillin/tazobactam, ceftazidime and amikacin was only 37.5%. As opposed to *P. aeruginosa*, other GN bacteria were 100% sensitive to ceftazidime and amikacin, except for the extended spectrum of beta-lactamase (ESBL) bacteria and *Stenotrophomonas maltophilia*, as

Table 1. Demographic data of 146 patients with 305 episodes of febrile neutropenia

Data	Number (%) (N=305)
Age (years) (mean ± SD)	6.5 ± 4.4
Range of age (years)	
< 5	117 (38.4)
5-10	108 (35.4)
10-15	78 (25.6)
> 15	2 (0.7)
Male: female (%)	61.3: 38.7
Type of malignancies	
ALL	136 (45.6)
ANLL	62 (20.3)
Solid tumors	59 (19.3)
Lymphoma	45 (14.8)
WBC (cells/mm³) (median; range)	3,903.7 (100-259,000)
ANC (cells/mm³) (median; range)	218.4 (0-992)
ANC at diagnosis of FN (cells/mm³)	
< 500	248 (81.3)
500-1,000	57 (18.7)
Type of infection	
Community acquired infection	248 (81.3)
Hospital acquired infection	57 (18.7)

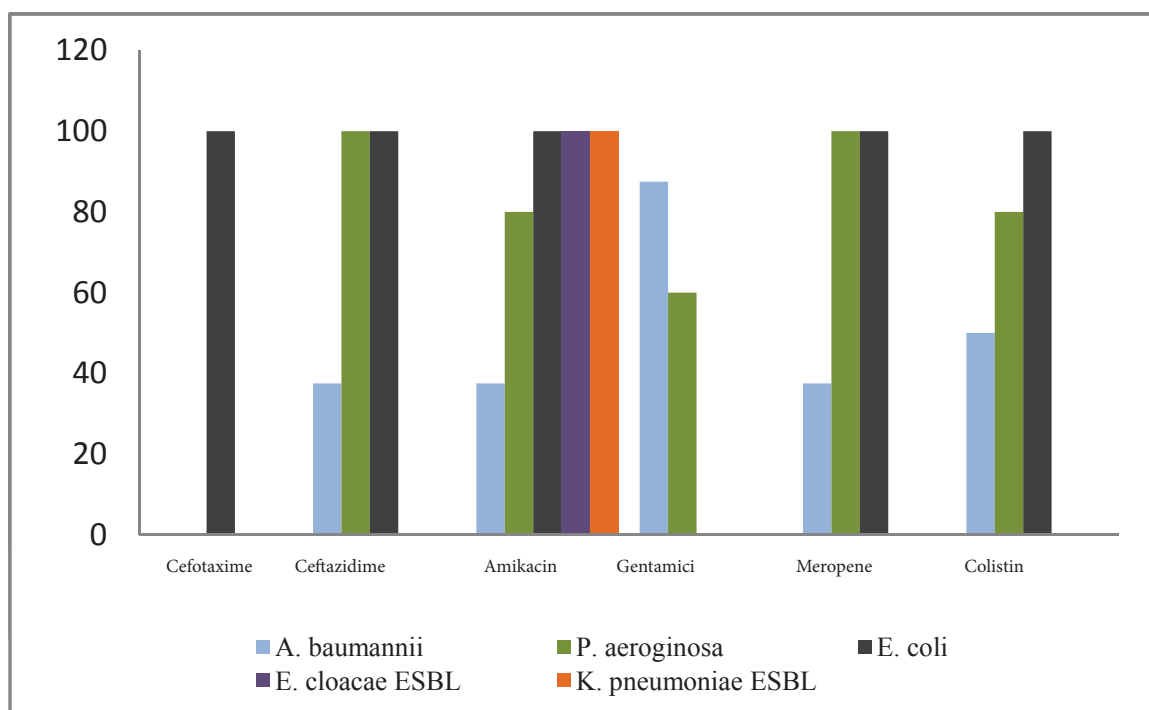
Table 2. Symptoms and signs of patients when febrile neutropenia was diagnosed.

Symptoms and signs when febrile neutropenia was diagnosed	Number (%) (N = 305)
Peak temperature within 24 hours after diagnosis of FN (°C) (mean ± SD)	39.1 ± 0.68
Non-specific symptoms	140 (45.9)
Symptoms of upper respiratory tract infection	82 (27.2)
Symptoms of gastrointestinal infection	41 (13.8)
Skin lesions	24 (7.9)
Oral lesions	18 (5.9)
Symptoms of lower respiratory tract infection	12 (3.9)
Hypotension	1 (0.3)
Other	8 (2.6)

shown in Figure 1. The cure rate of treatment with the current guideline of antibiotic use was 94.1%. However, the mortality rate of patients with *A. baumannii* septicemia was 50%. One pa-

Table 3. Risk factors of positive hemoculture in patients with febrile neutropenia

Risk factors	Number of hemoculture			p-value
	Number (%) (N=305)	Positive (N=30)	Negative (N=275)	
Nasogastric tube	13 (4.3)	6	7	<0.000
Endotracheal tube	10 (3.3)	6	4	<0.000
Admission in intensive care unit	12 (3.9)	7	5	<0.000
Urinary catheter	12 (3.9)	6	6	<0.000
Surgery	8 (2.6)	1	7	0.851
Central intravenous catheter	9 (3.0)	5	4	<0.000
Total parenteral nutrition	1 (0.3)	0	1	0.732

**Figure 1.** Sensitivity of GN bacteria to antibiotics

tient with community acquired *E. coli* bacteremia was sensitive to all tested antibiotics. Both patients with GP bacteremia were sensitive and also susceptible to the entire antibiotics tested.

Ninety four percent of patients were cured within the recent guideline of empirical antibiotic use in FN. Only 4.6% of patients died from

infection, while 1.3% passed away from other causes. Twenty nine percent of patients obtained granulocyte colony stimulating factor (G-CSF). A mortality rate of 10% from infection in patients receiving G-CSF was significantly higher ($p=0.018$) than the death rate of patients who did not get G-CSF (2.9%).

Discussion

The rate of bacteremia in patients with FN in this study was 10%, which did not differ from previous studies in Thailand or other countries (4-16%) [5, 6, 8, 9]. GN bacteria were still the most common causative organisms in our and other institution [7, 12]. However, the most common types of bacteria have changed over time. In this study, three of the most common organisms were *A. baumannii*, *P. aeruginosa* and *E. coli*, consecutively, while a previous study reported *P. aeruginosa*, *E. coli* and Enterobacter spp., consecutively [7]. According to the recent guideline for FN, the common bacteria may be shifted, due to the high efficacy of empirical antibiotics. Therefore, most bacteria were eliminated, while *A. baumannii* is usually resistant to most antibiotics in general use, was found more commonly in this study. This incidence was the same as that in a recent study at Chulalongkorn Memorial Hospital [13], and many centers in Thailand and western countries [14-17].

Patients with *A. baumannii* bacteremia tend to have more severe symptoms and a higher mortality rate. In this study, four from eight patients (50%) with *A. baumannii* infection died. This mortality rate is approximate to that in a previous study of *A. baumannii* infection in non-neutropenic adult patients [18]. *A. baumannii* is usually sensitive only to colistin, which is not used commonly as an empirical antibiotic. Most patients receive colistin after culture results show *A. baumannii*. Then it might be too late to start this antibiotic because patients would already have had more severe clinical manifestation. In this study, the risk factors of *A. baumannii* infection were ICU admission, central venous catheterization, and nasogastric and endotracheal intubation, which were the same as in the study by Baran et al [18]. Endotracheal intubation [19] and ICU stay [18, 20] were determined as risks of death in patients with carbapenem-resistant *A. baumannii* infection. *A. baumannii* was found frequently also in patients with respiratory tract

infection [21]. However, the number of patients infected with *A. baumannii* was not enough to identify the isolated risk factor of *A. baumannii* infection in this study.

In this study, the rate of GP bacteremia was much less than that in previous studies in western countries, as shown in Table 4. The rate of GP infection was lower in Thailand than in those reports from western countries because the rate of long-dwelling central line catheterization [22] was not prevalent in Thailand [8, 9]. However, if patients have any symptoms of severe mucositis; skin and soft tissue infection; or other risk factors of GP infection, including hemodynamic instability, radiography-confirmed pneumonia or central line catheterization with signs of infection; antibiotics against GP bacteria should be added [23]. Ceftazidime and amikacin are still effective empirical antibiotics in oncologic pediatric patients with FN because their sensitivity to *P. aeruginosa* and *E. coli* is 100%. Meropenem also is sufficient for eradicating most GN bacteria, except *A. baumannii* bacteremia.

The mortality rate from infection among patients with FN was 4.6% in this study, which was the same as in previous studies that used similar empirical antibiotics, including ceftazidime and amikacin as first line therapy and carbapenem for second line therapy [6, 7]. This result confirms that the current treatment guideline for FN is still effective. However, carbapenem and colistin should be administered early in order to decrease the mortality rate from *A. baumannii* bacteremia in pediatric patients with FN. These patients are at risk of *A. baumannii* infection from ICU admission, central venous catheterization, and nasogastric and endotracheal intubation until all culture results are revealed.

FN patients who received G-CSF had a higher mortality rate than those who did not receive it. This result might be explained by the rationale of G-CSF use. During the time of this study, G-CSF was used only in patients with FN who had severe infection, such as positive blood culture, hypotension and severe pneumonia. Therefore, these patients had more severe clinical symp-

Table 4. Comparison of previous studies to this study

Data	Studies		
	Hakim H	Agyeman P	This study
Place	Saint Jude Children's Research Hospital	Pediatric oncology centers	Chiang Mai University Hospital
Country	United States of America	Switzerland and Germany	Thailand
Type of study	Prospective	Prospective	Retrospective
Year of study	2004-2005	2004-2007	2007-2009
Age (year; range)	2.4-21.6	1-18	0.1-18
Median age (year)	5.9	6.9	6.6
Number of population	337	206	146
Number of positive blood culture	41	73	30
Type of bacteria (%)			
GP bacteria	39	63	6.7
GN bacteria	61	37	86.7
Top three of organisms found (%)			
1 st rank	<i>S. viridans</i> (29)	Coagulase-negative <i>Staphylococci</i> (21.9)	<i>A. baumannii</i> (26.7)
2 nd rank	<i>E. coli</i> (12)	<i>E. coli</i> (20.5)	<i>P. aeruginosa</i> (16.7)
3 rd rank	<i>P. aeruginosa</i> (10)	<i>Streptococcus mitis</i> (16.4)	<i>E. coli</i> (10)

toms than other groups. There was no usage of prophylactic G-CSF at that time. According to Smith et al, G-CSF should be started for oncologic patients as a primary prophylaxis for FN, when the rate of FN is greater than 20%, due to chemotherapy [23-25]. Hence, patients with AML, lymphoma or solid tumor are supposed to receive primary G-CSF prophylaxis to decrease the rate of serious infection.

In conclusion, *A. baumannii* is an emerging organism of FN among oncologic pediatric patients in CMU Hospital. Even though most patients without bacteremia still have a high response to the current treatment guideline for FN, carbapenem and colistin should be given early to patients at risk of *A. baumannii* bacteremia, in order to reduce the mortality rate from *A. baumannii* infection.

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เชื้อที่เป็นสาเหตุและแบบแผนความไวของเชื้อต่อยาปฏิชีวนะในผู้ป่วยเด็กโรคมะเร็งที่มีภาวะใช้ร่วมกับเม็ดเลือดขาวชนิดนิวโทรฟิลต่ำ ในโรงพยาบาลมหาราชนครเชียงใหม่ในระหว่าง ปี พ.ศ. 2550-2552

อัญชลี วัจจิระพันธ์, พ.บ., รุ่งโรจน์ เนตรศิรินิลกุล, พ.บ., ภัทรา ธนรัตนากร, พ.บ., และ
พิมพ์ลักษณ์ เจริญขวัญ, พ.บ.
ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

วิธีการวิจัย การศึกษาแบบย้อนหลังในผู้ป่วยเด็กอายุต่ำกว่า 18 ปีที่ได้รับการวินิจฉัยเป็นโรคมะเร็งและเข้ารับการรักษาในหอผู้ป่วยกุมารเวชกรรม โรงพยาบาลมหาราชนครเชียงใหม่ ร่วมกับมีภาวะใช้ร่วมกับเม็ดเลือดขาวชนิดนิวโทรฟิลต่ำ ระหว่างเดือนมกราคม พ.ศ. 2550 ถึงเดือนธันวาคม พ.ศ. 2552

ผลการศึกษา มีผู้ป่วยทั้งหมด 146 รายที่ได้รับการวินิจฉัยภาวะใช้ร่วมกับเม็ดเลือดขาวชนิดนิวโทรฟิลต่ำจำนวน 305 ครั้ง โรคมะเร็งที่พบได้บ่อยที่สุด คือ มะเร็งเม็ดเลือดขาวเฉียบพลันชนิดลิมโฟบลาสต์ (ร้อยละ 45.6) พบการติดเชื้อในกระแสเลือดจากการเพาะเชื้อจำนวน 30 ครั้ง ผลการเพาะเชื้อในกระแสเลือดส่วนใหญ่เป็นแบคทีเรียแกรมลบ (ร้อยละ 86.7) โดยเชื้อแบคทีเรียที่พบบ่อย 3 อันดับแรก ได้แก่ *Acinetobacter baumannii* ร้อยละ 27.6, *Pseudomonas aeruginosa* ร้อยละ 16.7 และ *Escherichia coli* ร้อยละ 10 ตามลำดับ เชื้อ *Acinetobacter baumannii* ซึ่งมีความไวต่อยา colistin ถึงร้อยละ 88 แต่มีความไวต่อยา piperacillin/tazobactam, ceftazidime และ amikacin เพียงร้อยละ 37.5 ส่วน *Pseudomonas aeruginosa* และแบคทีเรียแกรมลบที่ไม่ใช่กลุ่ม extended spectrum beta-lactamase (ESBL) และ *Stenotrophomonas maltophilia* ยังคงมีความไวต่อยา ceftazidime และ amikacin ร้อยละ 100 พบอัตราการตอบสนองต่อแนวทางการรักษาผู้ป่วยเด็กภาวะใช้ร่วมกับเม็ดเลือดขาวชนิดนิวโทรฟิลต่ำในโรงพยาบาลมหาราชนครเชียงใหม่ที่ใช้ในปัจจุบันถึงร้อยละ 94.1 อย่างไรก็ตาม อัตราตายจากการติดเชื้อ *Acinetobacter baumannii* สูงถึงร้อยละ 50 (4 ใน 8 ราย)

สรุปผลการศึกษา *Acinetobacter baumannii* เป็นสาเหตุของภาวะใช้ร่วมกับเม็ดเลือดขาวชนิดนิวโทรฟิลต่ำในผู้ป่วยเด็กโรคมะเร็งในโรงพยาบาลมหาราชนครเชียงใหม่ที่พบได้บ่อยขึ้น แม้ว่าทำให้ยาปฏิชีวนะตามแนวทางการรักษาผู้ป่วยเด็กที่มีภาวะใช้ร่วมกับเม็ดเลือดขาวชนิดนิวโทรฟิลต่ำที่ใช้ในปัจจุบันยังมีประสิทธิภาพสูง แต่การให้ยากุ่ม carbapenem และ colistin ตั้งแต่เริ่มต้นในผู้ป่วยที่มีความเสี่ยงในการติดเชื้อ *Acinetobacter baumannii* ในกระแสเลือดจะช่วยลดอัตราการตายจากการติดเชื้อดังกล่าว **เชียงใหม่เวชสาร 2555;51(3):71-78.**

คำสำคัญ: ภาวะใช้ร่วมกับเม็ดเลือดขาวชนิดนิวโทรฟิลต่ำ เด็ก มะเร็ง การติดเชื้อในกระแสเลือด เชื้อ *Acinetobacter baumannii*