

## Febrile neutropenia in Chulalongkorn Hospital during 1994-1995

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Hiransuthikul N, Tantawichien T, Suwangool P, Nuchprayoon T. Febrile neutropenia in Chulalongkorn Hospital during 1994-1995. *Chula Med J* 1996 Oct;40(10): 781-99

**Objective** : *To identify the prevalence and source of infection, the etiologic pathogens and the outcome of febrile neutropenic patients admitted to Chulalongkorn Hospital during 1994-1995.*

**Setting** : *Medical records of febrile neutropenic patients who were admitted to Chulalongkorn Hospital from 1<sup>st</sup> January 1994 to 31<sup>st</sup> December 1995 were reviewed.*

**Research design** : *Retrospective chart review.*

**Patients** : *131 febrile neutropenic patients with an age range of 1-78 years (mean±SD = 29.6±19.4) were retrospectively chart reviewed.*

**Results** : *Of 131 febrile neutropenic patients admitted to Chulalongkorn Hospital during 1994 - 1995 there were 185 admissions and 212 total episodes of febrile neutropenia during hospitalization. The three most common primary diseases leading to neutropenia were post-chemotherapeutic ANLL, ALL and lymphoma (38.7%, 17.0%, and*

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11.3% respectively). Infection was found in 69.3% of the cases with 39.6% clinically documented infection and 29.7% microbiologically documented infection. Unexplained fever was found in 30.7%. Pneumonia was the most common source of infection (23.5%). Gram-negative bacteria was the major causative pathogen isolated (71.8%) and the most common was *Escherichiae coli* (23.9%). Blood cultures grew organisms in 16.5% of the febrile neutropenic episodes and the most common were *Pseudomonas aeruginosa* and *Klebsiella* spp. (17.1% each). The case-fatality rate was 20.3% and was significantly related to the presence of increased age, shorter duration of hospitalization and primary diseases leading to febrile neutropenia including aplastic anemia and lymphoma. There were no significant relationships between the fatalities and the lowest level of neutrophile count, the duration of neutropenia, the absolute neutrophile count <100 per cu.mm., the presence of bacteremia, and treatment with hematopoietic growth factors.

**Conclusions** : From retrospective chart reviews of febrile neutropenic patients admitted in Chulalongkorn Hospital, hematologic malignancy was the most common primary disease leading to neutropenia. The prevalence of infection was 69.3%. Pneumonia was the most common source of infection. Gram-negative bacteria were the most common causative pathogen found which was different from findings in many western countries. The prognosis was significantly related to age, duration of hospitalization and primary disease leading to febrile neutropenia

**Key words** : Febrile neutropenia, Prevalence, Infection, Blood cultures, Chulalongkorn Hospital.

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Received for publication. August 15, 1996.

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**วัตถุประสงค์** : เพื่อศึกษาอัตราความชุก และแหล่งของการติดเชื้อ, เชื้อที่เป็นสาเหตุ และผลการ ดูแลรักษาในผู้ป่วยที่มีไข้ร่วมกับภาวะเม็ดโลหิตขาวชนิดนิวโทรฟิลส์ต่ำ ซึ่งเข้าพักรักษาในโรงพยาบาลจุฬาลงกรณ์ ระหว่างปี พ.ศ. 2537-2538

**สถานที่ทำการศึกษา** : หน่วยเวชสถิติ โรงพยาบาลจุฬาลงกรณ์

**รูปแบบการวิจัย** : การศึกษาเชิงพรรณานายินย้อนหลัง โดยการทบทวนเวชระเบียนผู้ป่วยในผู้ป่วยที่ได้ทำการศึกษา: ผู้ป่วยที่มีไข้ร่วมกับภาวะเม็ดเลือดขาวชนิดนิวโทรฟิลส์ต่ำที่เข้าพักรักษาในโรงพยาบาลจุฬาลงกรณ์ ตั้งแต่ 1 มกราคม 2537 ถึงวันที่ 31 ธันวาคม 2538 จำนวน 131 คน ซึ่งมีพิสัยของอายุตั้งแต่ 1-78 ปี (ค่ามัชฌิมเลขคณิต  $\pm$  ค่าเบี่ยงเบนมาตรฐาน =  $29.6 \pm 19.4$ ) ได้รับการศึกษาเวชระเบียนผู้ป่วยในย้อนหลัง

**ผลการศึกษา** : ผู้ป่วยที่มีไข้ร่วมกับภาวะเม็ดโลหิตขาวชนิดนิวโทรฟิลส์ต่ำ 131 ราย ในระหว่างปี 2537-2538 ได้เข้าพักรักษาในโรงพยาบาลจุฬาลงกรณ์ 185 ครั้ง และมีไข้ร่วมกับภาวะเม็ดโลหิตขาวชนิดนิวโทรฟิลส์ต่ำเกิดขึ้น 212 ครั้ง โรคปฐมภูมิที่เป็นสาเหตุของภาวะเม็ดโลหิตขาว ชนิดนิวโทรฟิลส์ต่ำ ซึ่งพบมากที่สุด 3 อันดับแรก คือ มะเร็งเม็ดโลหิตขาว ชนิด ANLL, ALL และ lymphoma หลังได้รับเคมีบำบัด (พบร้อยละ 38.7, 17.0, และ 11.3 ตามลำดับ) โรคติดเชื้อพบเป็นสาเหตุของไข้ ร้อยละ 69.3 โดยเป็นการติดเชื้อที่วินิจฉัยจากอาการ และ/หรืออาการแสดง ทางคลินิก ร้อยละ 39.6 และเป็นการติดเชื้อที่พบเชื้อก่อโรคจากการตรวจทางจุลชีววิทยา ร้อยละ 29.7 พบไข้ไม่ทราบสาเหตุ ร้อยละ 30.7 ปอดบวมเป็นโรคติดเชื้อที่พบบ่อยที่สุด (ร้อยละ 23.5) เชื้อแบคทีเรียแกรมลบ เป็นเชื้อก่อโรคที่พบเป็นส่วนใหญ่ (ร้อยละ 71.8) และ *Escherichiae coli* เป็นเชื้อแบคทีเรียที่พบบ่อยที่สุด (ร้อยละ 23.9) การเพาะเชื้อจากโลหิต พบเชื้อก่อโรค ร้อยละ 16.5 ของภาวะไข้ และเชื้อก่อโรคที่พบมากที่สุด คือ *Pseudomonas aeruginosa* และ *Klebsiella spp.* (พบอย่างละ ร้อยละ 17.1) ผู้ป่วยที่มี

ใช้ร่วมกับภาวะเม็ดโลหิตขาวชนิดนิวโทรฟิลล์ต่ำ มีอัตราการตายร้อยละ 20.3 และพบว่าอัตราการตายจะสูงกว่าอย่างมีนัยสำคัญ ในผู้ป่วยที่มีอายุมากกว่า ระยะเวลาที่อยู่ในโรงพยาบาลสั้นกว่า และโรคประจําภูมิที่เป็นสาเหตุของภาวะเม็ดโลหิตขาวชนิดนิวโทรฟิลล์ต่ำ ได้แก่ aplastic anemia และ lymphoma ไม่พบความสัมพันธ์ระหว่างอัตราการตาย และระดับต่ำสุดของเม็ดโลหิตขาว ชนิดนิวโทรฟิลล์, ระยะเวลาที่เม็ดโลหิตขาว ชนิดนิวโทรฟิลล์ต่ำ, ภาวะเม็ดโลหิตขาวชนิดนิวโทรฟิลล์ต่ำกว่า 100 ต่อ ลบ.มม., การพบเชื้อในกระแสโลหิตและการได้รับ hematopoietic growth factors./

**วิจารณ์และสรุป** : จากการศึกษาย้อนหลังโดยการทบทวนเวชระเบียนผู้ป่วยใน ของผู้ป่วยที่มีภาวะใช้ร่วมกับภาวะเม็ดโลหิตขาวชนิดนิวโทรฟิลล์ต่ำ ซึ่งเข้าพักรักษาในโรงพยาบาลจุฬาลงกรณ์ พบว่ามะเร็งของระบบโลหิต เป็นสาเหตุของภาวะเม็ดโลหิตขาวชนิดนิวโทรฟิลล์ ต่ำที่พบมากที่สุด พบอัตราความชุกของการติดเชื้อร้อยละ 69.3 โรคติดเชื้อที่พบบ่อยที่สุด ได้แก่ปอดบวม เชื้อแบคทีเรียกรัมลบ ยังเป็นเชื้อก่อโรคที่พบบ่อยที่สุด ซึ่งแตกต่างจากที่พบในการศึกษาของประเทศทางตะวันตก การพยากรณ์โรค ขึ้นอยู่กับอายุ ระยะเวลาที่อยู่ในโรงพยาบาล และโรคประจําภูมิที่เป็นสาเหตุของภาวะเม็ดโลหิตขาวชนิดนิวโทรฟิลล์ต่ำ

Infections remain a major concern in the management of patients with febrile neutropenia. During the past two decades, the importance of promptly initiating therapy with broad spectrum antimicrobial drugs whenever a neutropenic patient becomes febrile has been well recognized and considered a standard treatment. The use of empirical antimicrobial therapy for gram-negative bacillary infection has significantly reduced the morbidity and mortality associated with untreated infections in febrile neutropenic patients.<sup>(1-3)</sup> However, a number of factors related to the use of this empirical therapy have changed over the past decade. Among these are alterations in the patterns of infections and the causative pathogens, particularly the increasing prevalence of infections due to gram-positive bacteria. In many centers around the world, both coagulase-negative and coagulase-positive staphylococci and streptococci (including viridans streptococci) have emerged as the most frequent pathogens.<sup>(4-6)</sup> In spite of the changing pattern of infection, the predominant pathogens at a particular center have the most impact on the type of antibiotics that are selected for empiric antimicrobial therapy. In Chulalongkorn Hospital the empiric antimicrobial therapy for febrile neutropenic patients during recent years was a combination of  $\beta$ -lactam antibiotics or quinolones and aminoglycosides for covering gram-negative bacteria, particularly *Pseudomonas aeruginosa*. However, there was no supporting data about the predominant causative pathogens and the outcome of the febrile neutropenia in Chulalongkorn Hospital. Therefore, we retrospectively studied the febrile

neutropenic patients admitted to Chulalongkorn Hospital during 1994-1995 in order to identify the prevalence and source of infection, the etiologic pathogens and the outcome of the febrile neutropenia.

## Materials and Methods

The medical records of patients who developed fever and were found to have absolute neutropenia during hospitalization at Chulalongkorn Hospital between 1<sup>st</sup> January 1994 and 31<sup>st</sup> December 1995 were reviewed.

### Inclusion criteria

Patients were included in the study after the medical records review if they had fever  $> 38.0^{\circ}\text{C}$  measured orally at least twice 4 hours apart in a day, or a single value of  $38.3^{\circ}\text{C}$  and had an absolute neutrophil count of  $< 500$  polymorphonuclear leukocytes and bands per cubic millimeter. Patients with hematologic malignancies who were receiving consolidation or maintenance therapy or hematopoietic growth factors (G-CSF or GM-CSF) were also included.

### Exclusion criteria

Patients were excluded from the study if:

1. After medical records review the primary disease that caused a neutropenia could not be identified.
2. Blood culture during the febrile neutropenic episode was not conducted.

### Operational definition

Each febrile episode was classified as either a clinically or microbiologically documented infection or unexplained fever. This criteria was

the same as the definitions according to "The General Guideline for The Evaluation of New Anti-infective Drugs for The Treatment of Febrile Episodes in Neutropenic Patients"<sup>(7)</sup> and those of Pizzo et al<sup>(8)</sup> as follows:

1. Microbiologically documented infection

Isolation of a bacterial or fungal pathogen from blood, bone marrow, urine, pus, or exudates, along with clinical, other laboratory, or radiographic evidence of infection were required.

Two broad categories may be defined by microbiologic criteria.

1.1 Bacteremia or fungemia involving one or more organisms, without a definable non-hematogenous site of infection.

1.2 Infection at a specific site (e.g. pneumonia, abscess, urinary tract infection, otitis media) with or without concomitant bacteremia or fungemia.

2. Clinically documented infection

Infection diagnosed at a certain site but the site is inaccessible or the microbial etiology cannot be proven, including contamination from normal flora. This category included cellulitis, culture-negative pneumonia, necrotizing oral mucositis and marginal gingivitis, anal and perianal infection.

3. Unexplained fever

Fever accompanied by neither clinical nor microbiological evidence of infection.

### Statistical Analysis

Statistical tests included Chi-square or Fisher's exact test for discrete variables and Student's t-test for continuous variables.

### Results

During the two-year study period, 150 febrile neutropenic patients were admitted to Chulalongkorn Hospital. But only 131 medical records could be located. There were 106 adults and 25 children with 78 males and 53 females. The range of age was 1-78 years old with a mean + SD = 29.6 + 19.4. Of the 131 patients there were 185 admissions and 212 total episodes of febrile neutropenia during their hospitalization.

The primary diseases leading to neutropenia are shown in Figure 1. Hematologic malignancy was a major group, 77.4% (ANLL 44.4%, ALL 17.5% lymphoma 11.8%, CML 2.8% and CLL 0.9%). The three most common primary disease were ANLL, post-chemotherapy (38.7%); ALL, post-chemotherapy (17.0%) and lymphoma, post-chemotherapy (11.3%). Other primary diseases were solid tumor (9.9%), all of which developed neutropenia after receiving chemotherapy; Aplastic anemia, (5.7%); Agranulocytosis (2.8%); Myelofibrosis, AIDS and myelodysplastic syndrome (0.9% each); Malignant histiocytosis, disseminated tuberculosis and SLE (0.5% each).

During the 212 febrile neutropenic episodes, infection was found in 69.3% (147 episodes) with clinically documented infection in 39.6% (84 episodes) and microbiologically documented infection in 29.7% (63 episodes) Unexplained fever was found in 30.7% (65 episodes) (Figure 2).

Sources of infection are shown in Figure 3. Pneumonia was the most common source of infection (23.5%). It should be noted that the five leading sources of infection (pneumonia, bacteremia

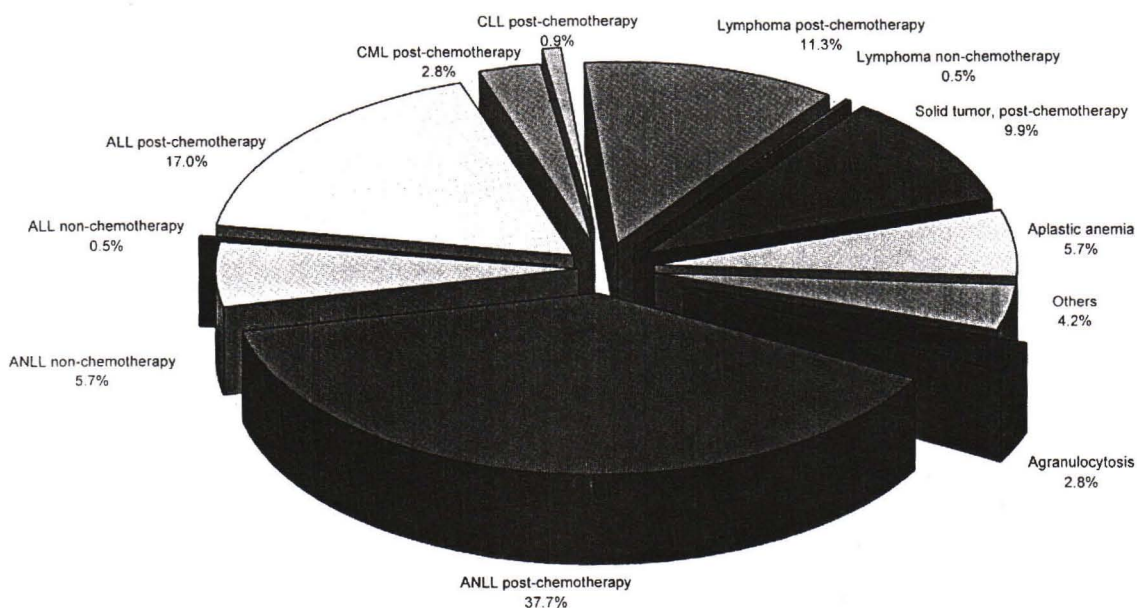


Figure 1. Primary disease leading to neutropenia in 212 febrile neutropenic episodes.

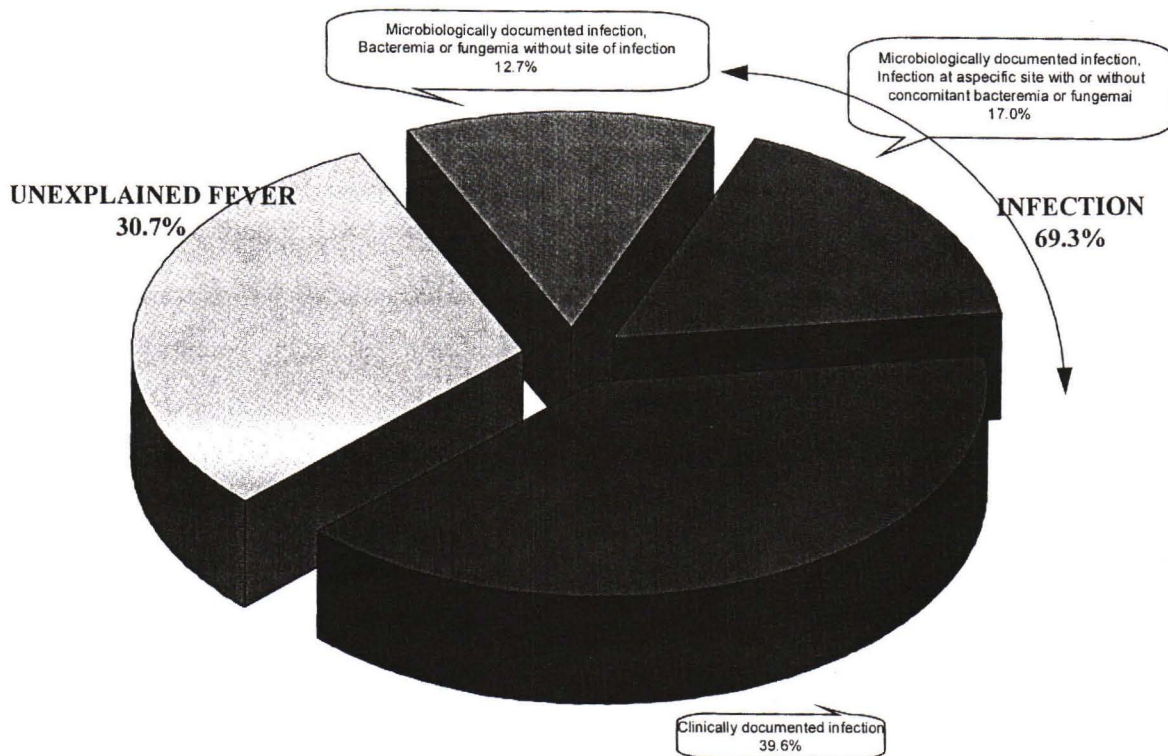
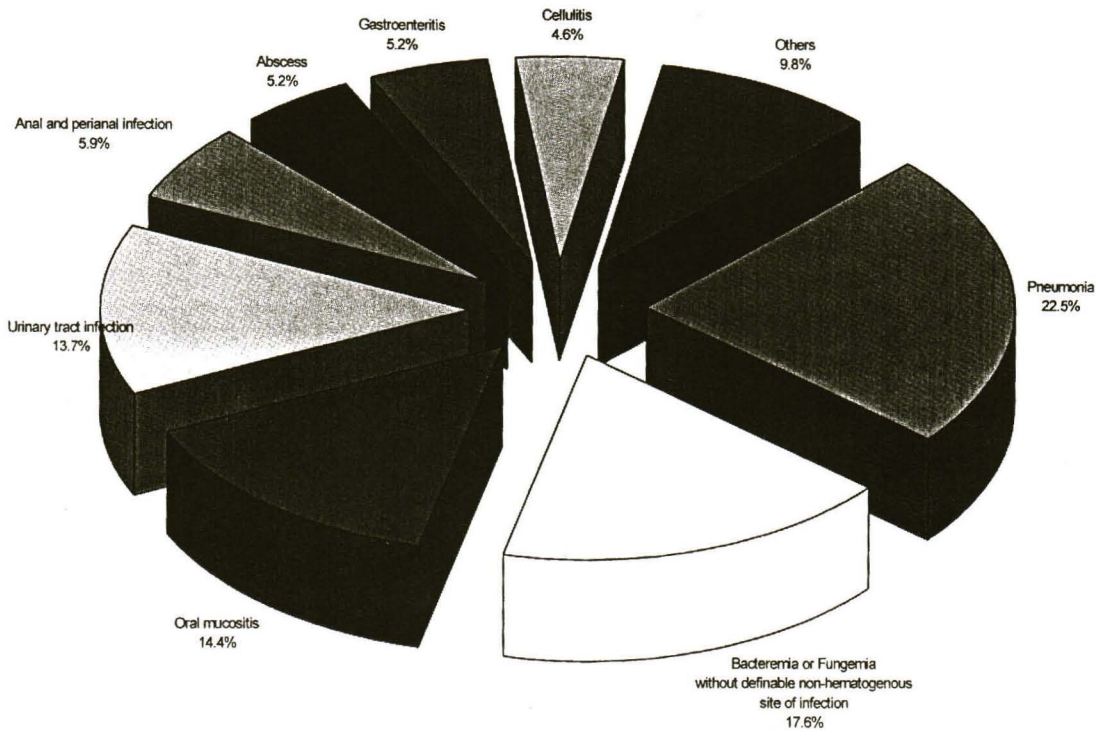


Figure 2. Causes of fever in 212 febrile neutropenic episodes.

or fungemia without definable non-hematogenous sites of infection, oral mucocitis, urinary tract

infection and anal and perianal infection) amounted to 75% of all sources of infection.



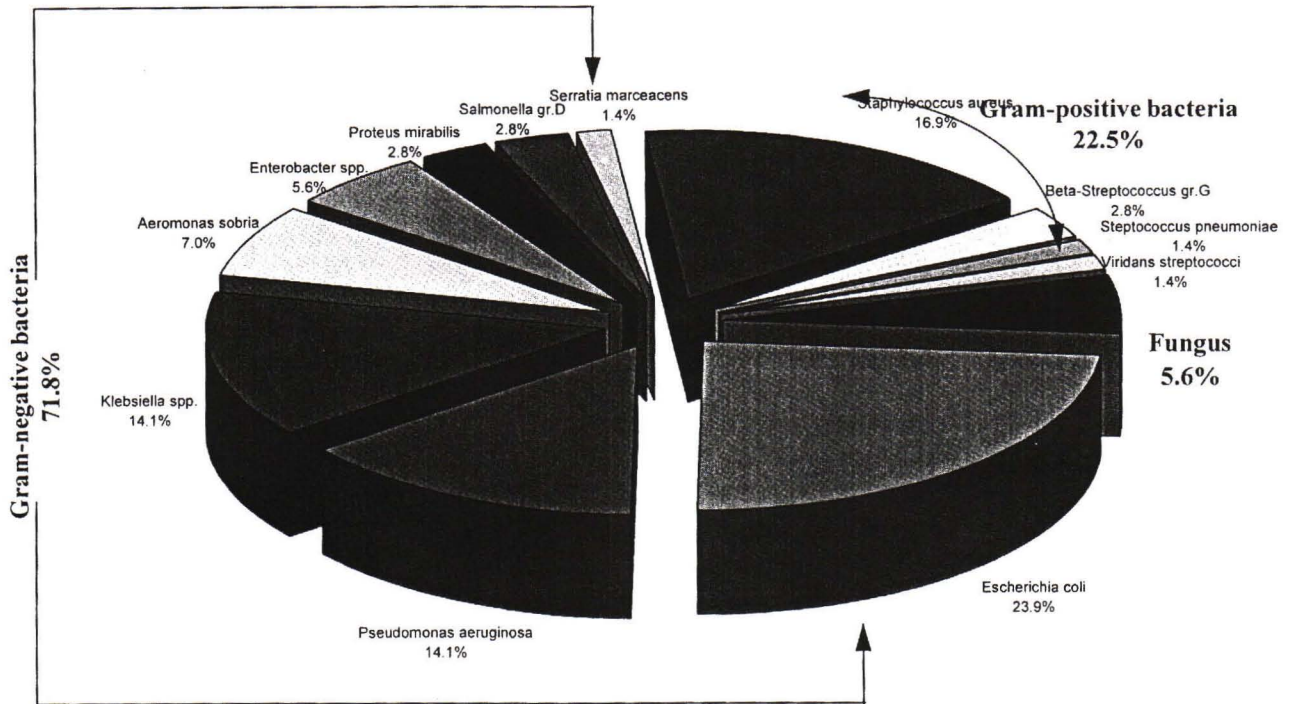
**Figure 3.** Sources of infection in 147 febrile neutropenic episodes.

Of the causative pathogens, gram-negative bacteria were still the most common organism isolated (71.8%). The most common gram-negative bacteria was *Escherichia coli* (23.9%) which was found mainly in urinary tract infections and bacteremia. *Pseudomonas aeruginosa* and *Klebsiella* spp. were the second most common gram-negative bacteria found (14.1% each). Gram-positive bacteria were isolated in 22.5%, of which *Staphylococcus aureus* was the most common organism found (16.9%). Fungus was found in only 1.9% (Table 1 and Figure 4).

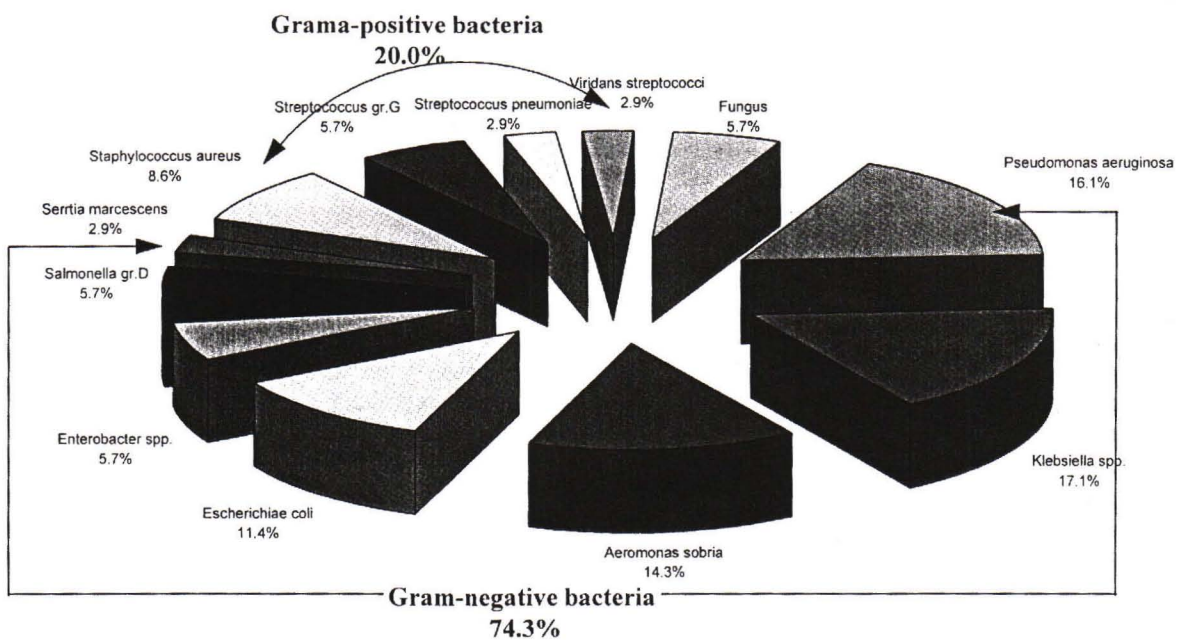
Blood cultures grew organisms in 16.5% (35 in 212 episodes of febrile neutropenia) and

gram-negative bacteria were still the most common organism isolated, 74.3%, whereas gram-positive bacteria and fungus were found in 20.0% and 5.7% respectively. *Pseudomonas aeruginosa* and *Klebsiella* spp. were the most common organisms found (17.1% each) (Table 2 and Figure 5). Blood cultures also grew *Staphylococcus epidermidis* for three intravenously catheterized patients. However, due to absence of other clinical and microbiological criterias suggestive of catheter related septicemia as in previous report<sup>(9,10)</sup> we could not consider them to be catheter-related bacteremia.





**Figure 4.** Causative pathogens in 63 febrile neutropenic episodes with microbiologically documented in fections.



**Figure 5.** Causative pathogens in 35 febrile neutropenic episodes with positive blood cultures.

**Table 1.** Microbiologically documented infection at a specific site and causative pathogens.

Organisms	Blood	Urinary tract	Resp. tract	Parotid gland	Ear	Skin & soft tissue	Liver	Total
<b>Gram-negative bacteria</b>								
- Escherichia coli	4	13	-	-	-	-	-	17
- Pseudomonas aeruginosa	6	2	-	-	-	2	-	10
- Klebsiella spp.	6	2	-	1	-	1	-	10
- Aeromonas sobria	5	-	-	-	-	-	-	5
- Enterobacter spp.	2	2	-	-	-	-	-	4
- Proteus mirabilis	-	2	-	-	-	-	-	2
- Salmonella gr.D	2	-	-	-	-	-	-	2
- Serratia marceacens	1	-	-	-	-	-	-	1
Total	26	21	-	1	-	3	-	51
<b>Gram-positive bacteria</b>								
- Staphylococcus aureus	3	-	-	1	2	6	-	12
- Streptococcus gr.G	2	-	-	-	-	-	-	2
- Streptococcus pneumoniae	1	-	-	-	-	-	-	1
- Viridans streptococci	1	-	-	-	-	-	-	1
Total	7	-	-	1	2	6	-	16
<b>Fungus</b>								
- Candida spp.	2	-	-	-	-	-	-	2
- Aspegillus spp.	-	-	1	-	-	-	-	1
- Not specify	-	-	-	-	-	-	1	1
Total	2	-	1	-	-	-	1	4
<b>All total</b>	<b>35</b>	<b>21</b>	<b>1</b>	<b>2</b>	<b>2</b>	<b>9</b>	<b>1</b>	<b>71</b>

\*27 cases were bacteremia or fungemia without site of infection and 8 cases were caused by urinary tract infection.

**Table 2.** Positive blood cultures in 212 febrile neutropenic episodes.

Organism	umber
<b>: Gram-negative bacteria</b>	
- pseudomonas aeruginosa	6
- Klebsiella spp.	6
- Aeromonas sobria	5
- Escherichiae coli	4
- Enterobacter spp.	2
- Salmonella gr.D	2
- Serrtia marcescens	1
Total	26
<b>: Gram-positive bacteria</b>	
- Staphylococcus aureus	3
- Streptococcus gr.G	2
- Streptococcus pneumoniae	1
- Viridans streptococci	1
Total	7
<b>: Fungus</b>	
Candida spp. (other than Candida albicans)	2
<b>All total</b>	<b>35</b>

For respiratory tract infections, after the medical records review we unfortunately could not differentiate the true pathogen from the bacterial colonization by non-invasive sputum examination and culture. Therefore, in these reviews, we could definitely isolate a causative pathogen in only one case. Aspergillus spp. was found by bronchoalveolar lavage (BAL) in a case of pneumonia.

Urine cultures were done for 195 of the 212 febrile neutropenic episodes and grew significant organisms in 20 specimens (19.6%). Escherichiae coli was the most common organism found (61.9%) (Table 1).

In skin and subcutaneous infections, pus from 5 subcutaneous abscesses grew organisms in every specimen with a single organism in 3 specimens (all were staphylococcus aureus) and 2 organisms in 2 specimens (Staphylococcus aureus + Pseudomonas aeuginosa and Staphylococcus aureus + Klebsiella spp.). Discharge and saline flush from 7 cases of cellulitis grew an organism in only 1 case (Staphylococcus aureus from cellulitis at the entry site of the subclavian catheter) Pseudomonas aeruginosa was isolated from pus culture from an infected scrotal ulcer in one case.

Aspiration of liver abscess in one case yielded fungus in a pathological specimen. Due to absence of a microbiological report, the fungus could not be specified.

The case-fatality rate of febrile neutropenia in our study was 20.3%. In analysis of the characteristics associated to the fatalities, we found that they were significantly related to a patient's increased age and shorter duration of hospitalization, but there were no significant relationship between the fatality and the level of lowest neutrophil count, the duration of neutropenia, the absolute neutrophil count < 100 per cu. mm., the presence of bacteremia and treatment with hematopoietic growth factors (Table 3).

**Table 3.** Characteristics of febrile neutropenia related to fatality.

Characteristics	Dead group (n = 43)	Survived group (n = 169)	P value
- Age, year (mean±S.D.)	37.3±19.6	27.9±19.1	<.05
- Duration of hospitalization, day (mean±S.D.)	30.4±26.6	59.9±48.9	<.05
- Lowest neutrophil count,per cu.mm (mean±S.D.)	140.71±23.8	151.41±44.3	NS
- Duration of neutropenia, days (mean±S.D.)	11.44±16.06	13.26±11.65	NS
- Neutrophil count < 100, episode	29	100	NS
- Bacteremia , episode	9	28	NS
- Adjunctive treatment growth factor,episode	15	42	NS

We also analysed the fatalities related to underlying diseases (Table 4). We found that the case-fatality rate was highest in aplastic anemia (41.7%), followed by lymphoma (36.0%) and solid tumor (28.6%). The case-fatality rate of ANLL and ALL, which were the two most common

primary diseases leading to neutropenia, were 10.6% and 13.5%, respectively (Table 4). But we found statistically significant higher case-fatality rate compared to overall death rate only in aplastic anemia, lymphoma and lower case-fatality rate in ANLL.

**Table 4.** Case-fatality related to primary diseases leading to neutropenia.

Primary disease leading to neutropenia	No. of case	Death	Case-fatality rate	P value
ANLL	94	10	10.6	<.05*
ALL	37	5	13.5	>.05
CML	6	1	16.7	>.05
CLL	2	1	50.0	>.05
Lymphoma	25	9	36.0	<.05*
Solid tumor	21	6	28.6	>.05
Aplastic anemia	12	5	41.7	<.05*
Agranulocytosis	4	2	50.0	>.05

## Discussion

Fever is a common occurrence in neutropenic patients, especially after cytotoxic chemotherapy. So, not surprisingly, in this study the most common primary diseases in which febrile neutropenia occurred were post-chemotherapeutic ANLL, ALL and lymphoma (38.7%, 17.0% and 11.3% respectively).

Infection is a major complication in febrile neutropenic patients. It was found that more than 60% of febrile illness in neutropenic patients, especially those with absolute neutrophil counts of less than 100 per cu.mm, was caused by infection<sup>(11)</sup>. In our study, infection was possibly a cause of fever in 72.2% but there was microbiologically-documented infection in only 32.6%. This is similar to several previous studies which found that infection was often difficult to document in neutropenic patients and approximately 40% of these patients were never found to have microbiologically documentable infection.<sup>(12)</sup> Nevertheless, most of these febrile episodes improved clinically after broad-spectrum antibiotic therapy, thus depicted the occult microbial sources as the cause of fever.<sup>(13,14)</sup>

The most common source of infection in our study was pneumonia (23.5%) followed by bacteremia or fungemia without a definable site of infection (17.6%), oral mucocitis (14.4%), urinary tract infection (13.1%) and anal and perianal infection (5.9%). It is noticeable that these sources of infection (except bacteremia or fungemia) added up to be about 60% of all sources of infection, which is similar to the EORTC (Euro-

pean Organization for Research on Treatment of Cancer) study<sup>(15)</sup>. Due to their simple diagnosis, these sources of infection should initially be considered and determined for early diagnosis and treatment. Due to a lower response rate to empiric antimicrobial therapy for patients with proven septicemia compared to those with clinically documented infections or unexplained fever, the importance of proper blood cultures and prompt empiric antimicrobial therapy is emphasized even though there might be no identifiable source of infection.<sup>(16-18)</sup>

The major causative pathogens in our febrile neutropenic patients were still gram-negative bacteria (71.8%), and the most common gram-negative bacteria isolated were *Escherichia coli* (23.9%) followed by *Pseudomonas aeruginosa* and *Klebsiella* spp. (14.1% each). Gram-positive bacteria were found in 22.5% of all causative organisms and *Staphylococcus aureus* was the most common organism found (16.9%). This data supports the findings of Suwanagool P., et al. in a multicenter study (including five university hospitals) which found that most of the causative pathogens in febrile neutropenia in Thailand were gram-negative bacilli, especially the *Enterobacteriaceae*.<sup>(19)</sup>

The sites of infection where pathogens were most frequently isolated was the blood. This might be due to the easy collecting of specimens and because blood cultures were done for all episodes of febrile neutropenia. We found bacteremia and fungemia in 16.5% of the febrile neutropenic episodes with 12.3% gram-negative

bacteria 3.3% gram-positive bacteria, and 0.9% candida (non-albicans) in the febrile neutropenic episodes, respectively. This finding is comparable to the EORTC Trial-I study during 1973-1978 which found 15.7% gram-negative and 5.8% gram-positive bacteremia in their febrile neutropenic patients.<sup>(17)</sup>

Two decades ago, most observations from large studies evaluating febrile episodes in neutropenic patients stressed the high incidence of gram-negative bacterial infection, particularly *Escherichia coli*, *Klebsiella pneumoniae* and

*Pseudomonas aeruginosa*.<sup>(17,18,20-22)</sup> However, since the early 1980's, most investigators in this field have pointed out the decreased incidence of septicemia caused by gram-negative bacteria and a significant increase in documented infections caused by gram-positive cocci, mainly streptococci, especially viridans streptococci.<sup>(21,23-25)</sup>

This was also the trend in the EORTC Trial VIII (1988-1990). They found that among 694 neutropenic patients, 15% had a single gram-positive bacteremia while 6.8% had a single gram-negative bacteremia (Table 5).<sup>(26,27)</sup>

**Table 5.** Single Gram-Negative Bacteriemia (SGNB) and Single Gram-Positive Bacteremia (SGPB) in Febrile, Granulocytopenic Patients.

		Percent with SGNB	Percent with SGPB
EORTC Trial I	(1973-1978)	15.7	5.8
EORTC Trial II	(1978-1980)	15.7	7.8
EORTC Trial III	(1980-1983)	12.9	9.0
EORTC Trial IV	(1983-1986)	14.5	10.1
EORTC Trial V	(1986-1988)	10.5	1.77
EORTC Trial VIII	(1986-1988)	6.8	15.0

Several hypothesis have been elaborated for this epidemiologic change. Prompt empiric antimicrobial therapy against gram-negative pathogens may be effective in decreasing the recovery rate of those pathogens, as deduced from blood cultures; improved prophylaxis using absorbable oral antibiotics (such as trimethoprim-sulfamethoxazole or quinolones) has also been shown effective in reducing the incidence of gram-nega-

tive bacillary septicemia.<sup>(28,29)</sup> However, the emergence and/or the selection of streptococci has been well documented. It is partially the result of extensive use of fluoroquinolones, agents poorly effective against *Streptococcus pneumoniae* and the viridans group of streptococci. In addition, other predisposing factors have been identified. Most patients treated with an intensive antineoplastic regimen for hematologic malignancy had at

least one central venous catheter or another intravascular device which constituted a source of infection caused mainly by staphylococci. Other potential sources of gram-positive cocci infections in febrile neutropenic patients have also been suggested, including the gastrointestinal tract and the oropharynx(28). Severe mucositis is more common in patients treated with current anti-neoplastic regimens, especially high-dose cytosine arabinoside, and therefore the mouth also represents an important source of infection by gram-positive cocci, particularly streptococci.

In our study, however, gram-negative bacteremia still predominated in febrile neutropenia. The reasons for this finding, which are different from western countries in the EORTC Trial VIII, may be due to 1) less use of intravascular devices in our febrile neutropenic patients, 2) fewer cases who underwent selective decontamination of endogenous gastrointestinal flora with co-trimoxazole or quinolones compound and, 3) fewer cases which received high-dose cytosine arabinoside. Further studies will be needed to prove these hypotheses.

For gram-positive bacteremia, we did not find any definite staphylococcal epidermidis bacteremia; however, a case of viridans streptococcal bacteremia with positive blood cultures in three separate specimens was found. This was a case of ANLL, post-chemotherapy (with cytosine arabinoside) who developed severe oral mucocitis and febrile neutropenia. Due to more frequent intravenous catheterization, increased cytosine arabinoside therapy for malignancy, and increased usage of oral quinolone prophylaxis in our

neutropenic patients in the future we should look for increased incidence of gram-positive bacteremia, especially staphylococcal and viridans streptococcal infection.

Fungal infections were found in four cases. One case was ANLL which developed prolonged and profound febrile neutropenia after chemotherapy despite multiple antibiotic treatments. Later, multiple liver abscesses were detected and an unspecified fungus (aspergillus-like?) was isolated from pathological specimens of liver aspiration. The result of culture for fungus was not recorded. However, the patient improved after a prolonged course of intravenous amphotericin-B treatment. Another case involved aspergillus pneumonia which occurred in a 38-year-old male, post-chemotherapeutic ANLL patient. He developed persistent febrile neutropenia despite prolonged antibiotic treatment. Later, there was a new pulmonary consolidation and aspergillus was isolated from transbronchial biopsy specimens. He improved gradually after intravenous amphotericin-B treatment with recovery of his granulocyte count.

Two cases of candidemia developed in post-chemotherapeutic ALL and aplastic anemia. Both had subclavian catheterization. They responded positively with intravenous amphotericin-B and catheter removal.

Febrile neutropenia, especially in malignant patients, is associated with a high mortality. Serious medical complications have been reported in 21% of cases and death in 4-30% of cases in large series<sup>(20,29-30)</sup>. The case-fatality rate for

febrile neutropenia in our study was about 20%, which is similar to a study at Songklanakarin University Hospital<sup>(31)</sup>. Factors that increased the risk of fatality in our study were:

- 1) Older age
- 2) Duration of hospitalization

We found that duration of hospitalization was significantly shorter among the mortality group which might be partly explained by the more severe medical status of this group.

Considering primary diseases leading to neutropenia, we found that aplastic anemia, lymphoma had a significantly poorer prognosis. In contrast ANLL had a significantly better outcome compared to overall death rate.

In this study, other potential risk factors such as duration of neutropenia, neutrophil count below 100 per cu. mm., bacteremia and treatment with hematopoietic growth factor could not be associated with the fatalities in our study. One explanation may be the intensive broad-spectrum antibiotics, including antifungal therapy, initiated very early when fever occurred in our neutropenic patients.

In conclusion, we have reported here a retrospective chart review of 212 febrile neutropenia episodes in Chulalongkorn Hospital during 1994-1995. The most common primary diseases leading to the neutropenia were post-chemotherapeutic ANLL, ALL and lymphoma, respectively. Infection was found in 69.3% of the cases with clinically documented infection in 39.6% and microbiologically documented infection 29.7%. Unexplained fever was found in 30.7%. The most

common source of infection was pneumonia. The causative pathogens were mainly gram-negative bacteria (71.8%) and the most common of these were *Escherichiae coli*. Blood cultures grew organisms in 16.5% of the cases with gram-negative bacilli still the most common pathogens isolated. The case-fatality rate was 20.3%. The prognosis was related to age, duration of hospitalization and primary disease leading to neutropenia.

### Acknowledgements

The authors wish to thank Mr. Krissadee Ditpradub for typing the manuscript and Mr. Thawatchai Mokkhawes for producing all of the figures in this study.

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