*Original Article*

# Changes in Etiologic Microorganisms in Thai Patients with Chemotherapy-Induced Neutropenia and Fever

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***Background:*** Infection in patients with chemotherapy-induced neutropenia is a serious complication that causes significant morbidity and mortality. Prompt and appropriate antimicrobial therapy improves treatment outcomes. However, mortality rate and complications in patients with febrile neutropenia were still high. Etiologic infectious agents of febrile neutropenia differ among countries and they change periodically.

***Objective:*** To identify the clinical characteristics and etiologic organisms in patients with febrile neutropenia at Siriraj Hospital, and to identify factors that significantly predict patient outcomes

***Materials and Methods:*** The medical records of patients with febrile neutropenia hospitalized at Siriraj Hospital between January 2008 and June 2010 were analyzed. Patient characteristics, epidemiologic data, bacteriologic data, and factors at the onset of fever were collected to predict patient outcomes. The data from this study was compared with data from a similar study conducted at our center in 2000.

***Results:*** Of 234 patients with 310 febrile neutropenic episodes, 80.8% had hematologic malignancies and 19.2% had solid tumors. Mean age of the 105 male and 129 female patients was 46.6±16.3 years. Patients recovered in 43.2% of cases, and the overall mortality rate was 19.7%. Bacteremia was found in 23.9% of cases. Gram-negative bacteria were the most common causative organisms. Compared with data from the study conducted in 2000, there was no significant change in the prevalence of Gram-negative and Gram-positive bacteria. The prevalence of extended-spectrum beta-lactamase [ESBL]-producing gram-negative bacteria is 29.8%. A significant increase in the prevalence of fungemia in febrile neutropenic patients was observed between the 2000 and 2010 study (0% to 6.7%, $p = 0.045$). Multivariate analysis revealed malignancy type, body temperature, and blood pressure to be factors that independently predict patient outcome.

***Conclusion:*** Consistent with the 2000 study finding, Gram-negative bacteria are still the most common etiologic organisms in febrile neutropenic patients at Siriraj Hospital. However, we found an increase in the proportion of ESBL-producing Gram-negative bacteria and fungal pathogens. Peak temperature of 39°C or higher and hypotension were identified as significant predictors of unfavorable outcomes, including death. Ongoing and vigilant surveillance of changing and emerging organisms is essential for optimizing patient outcomes.

***Keywords:*** Febrile neutropenia, Chemotherapy-induced neutropenia, Fever, Epidemiology, Neutropenic

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Neutropenia is a significant risk factor for serious infections, especially in individuals with leukemia or solid cancers who are receiving chemotherapy. Febrile neutropenic patients must be treated promptly and empirically with appropriate antibiotics to reduce mortality and morbidity. Nevertheless, infection is a leading cause of death in this patient population[(1)]. The mortality rate and incidence of complications in patients with febrile neutropenia was reported to be as high as 30%[(2)]. The Infectious Diseases Society of America [IDSA] has issued guidelines for the use of antibiotics in the treatment of febrile neutropenia[(3)]. The guideline recommendation is to treat all patients with a homogeneous regimen. Data from Europe and the United States show that Gram-negative bacteria, especially Enterobacteriaceae, accounted for approximately 60% to 70% of infections in febrile neutropenic patients. However, new evidence has emerged that the etiologic

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agents are increasingly Gram-positive bacteria[4] and other resistant organisms[5].

Although several studies in Western countries have been conducted to investigate the causative organisms and outcomes in febrile neutropenic patients[4-6], data from developing countries is lacking. A study conducted at Siriraj Hospital in Thailand[7] more than 10 years ago reviewed 147 patients with hematologic malignancies with 64 episodes of febrile neutropenia. They found that 22% of patients had bacteremia, and the most common causative pathogens identified from blood were Gram-negative bacilli (82% of all bacteremia), which is similar to studies by Anunnatsiri et al[8] and Chayakulkeeree and Thamlikitkul[9]. However, a more recent study conducted at Khon Kaen Hospital in Thailand[10] found a higher incidence of Gram-positive bacteria at 35.5%. Another study conducted at Siriraj Hospital in 2003[9] that involved 220 patients (72% had hematologic malignancies) with 267 episodes of febrile neutropenia found that burden of disease, control of cancer, duration of neutropenia, and dehydration to be factors that affect patient outcomes. Based on our review of the literature and to the best of our knowledge, no studies on the incidence of drug-resistant bacteria in chemotherapy-induced febrile neutropenia have been reported from Thailand.

The guideline for treatment of febrile neutropenia at Siriraj Hospital was developed based on previous data. However, the incidence of infection with Gram-positive and Gram-negative bacilli with extended-spectrum beta-lactamase [ESBL] has been increasing. The aim of this study was to identify the clinical characteristics and etiologic organisms in patients with febrile neutropenia at Siriraj Hospital, and to identify factors that significantly predict patient outcomes.

## Materials and Methods

### *Patients and data collection*

A retrospective chart review was performed in all patients older than 18 years diagnosed with febrile neutropenia and admitted to Siriraj Hospital between January 2008 and June 2010. The patients included had chemotherapy-induced febrile neutropenia according to American Society of Clinical Oncology and IDSA definition[3], which requires a single oral temperature of 38°C or higher for at least one hour with absolute neutrophil counts of less than 500 cells/mm$^3$ or less than 1,000 cells/mm$^3$ with a predicted decline to less than 500 cells/mm$^3$ over the following 48 hours. Patients with incomplete information, who died within 24 hours of admission, or who had neutropenia from other causes were excluded.

The data was extracted from patient medical records and included age, gender, body weight, height, body mass index, underlying cancer, comorbid diseases, number of courses and regimens of chemotherapeutic agents, use of growth factors and antibiotic prophylaxis, onset of fever at presentation, duration from the first day of the last episode of chemotherapy to hospitalization, duration of neutropenia, peak temperature, blood pressure, pulse rate, respiratory rate, clinical signs and symptoms at diagnosis of febrile neutropenia, antimicrobial agents, outcomes of treatment, and survival rate. Laboratory data included total leukocyte count, absolute neutrophil count, platelets, hemoglobin, blood urea nitrogen, creatinine, alanine transaminase [ALT], aspartate transaminase, total bilirubin, and albumin. Microbiological results and susceptibility profiles were also recorded. Raw data from the previous study conducted at our hospital[13] were used to compare the trend of etiologic microorganisms. The protocol for this study was approved by Siriraj Institutional Review Board [SIRB], Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

### *Definition of outcomes*

A favorable outcome was defined as a condition in which a patient became afebrile within five days after receiving treatment, and without serious complications. An unfavorable outcome was defined as a condition in which a patient died, changed antibiotics, or remained febrile for more than five days after receiving treatment.

### *Statistical analysis*

Patient characteristics are described as mean ± standard deviation, median and range, or frequency and percentage. Comparison in prevalence of organisms between the 2000 and 2010 study was performed using Chi-square test for trend. Univariate analysis was performed using t-test or Mann-Whitney U test for continuous variables, and Chi-square test for categorical variables. A multiple logistic regression model was used for multivariate analysis. SPSS Statistics version 13.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. For all tests, a two-tailed *p*-value of less than 0.05 was considered statistically significant.

## Results

The medical records of patients representing 385 episodes of febrile neutropenia between January 2008 and June 2010 were identified. Three hundred ten episodes from 234 patients met the criteria for this

study. Seventy-five episodes were excluded because of inadequate data (44 episodes), not meeting IDSA criteria (6 episodes), neutropenia from other causes (21 episodes), and death within 24 hours (4 episodes).

One hundred five patients (44.9%) were male. Mean age of patients was 46.6±16.3 years (range 14 to 78). One hundred eighty-nine patients (80.8%) had hematologic malignancies, of which acute leukemia (107 patients, 45.7%) and lymphoma (72 patients, 30.8%) were the most common. The other 45 patients (19.2%) had solid tumors, including breast cancer in 21 patients (9%) and gastrointestinal tract cancers in seven patients (3%). One hundred eighty-three (59%) episodes received growth factors and 49 episodes (15.8%) received antibiotic prophylaxis. Trimethoprim/sulfamethoxazole and levofloxacin were the most commonly prescribed prophylactic antimicrobials.

The most common sites of infection in patients with clinically documented infection were lung (10.6%), soft tissue (6.1%), urinary tract (4.8%), and gastrointestinal tract (4.8%). The source of infection was unknown in 179 episodes (57.7%). One hundred nineteen episodes (38.4%) with culture-proven data were classified as microbiologically documented infection, and 74 (23.9%) of those had bacteremia. Types of organisms isolated from blood are shown in Table 1. Most (57 specimens, 77%) of the causative organisms were Gram-negative bacteria, with Gram-positive bacteria found in 12 episodes (16.3%) and fungi found in five episodes (6.7%). The prevalence of ESBL-producing gram-negative bacteria is 29.8%. Compared with data from the 2000 study, there were increases in the prevalence of infection caused by fungi (Table 2).

The initial antimicrobial drugs prescribed are shown in Table 3. The most commonly used antimicrobial regimen was ceftazidime plus amikacin (64.8%), followed by piperacillin/tazobactam (12.3%), imipenem (7.1%), and meropenem (6.8%). Antimicrobial coverage is shown in Table 4. Ceftazidime monotherapy yielded the lowest coverage (74.1%), with imipenem delivering the highest coverage (91.1%). Ceftazidime

**Table 1.** Pathogens isolated from blood cultures from neutropenic patients

| Organism | Blood culture, n (%) |
|---|---|
| Gram-negative bacteria | 57 (77.0) |
| *Klebsiella pneumonia* | 19 (25.7) |
| *Escherichia coli* | 15 (20.2) |
| *Pseudomonas aeruginosa* | 9 (12.2) |
| *Aeromonas hydrophila* | 5 (6.7) |
| *Acinetobacter baumannii* | 4 (5.4) |
| *Proteus mirabilis* | 1 (1.4) |
| *Klebsiella oxytoca* | 1 (1.4) |
| Others | 3 (4.0) |
| Gram-positive bacteria | 12 (16.3) |
| MRSA | 3 (4.0) |
| MSSA | 2 (2.7) |
| Group G streptococci | 1 (1.4) |
| *Streptococcus pneumoniae* | 1 (1.4) |
| *Enterococcus faecium* | 1 (1.4) |
| *Bacillus* spp. | 1 (1.4) |
| Others | 3 (4.0) |
| Fungus | 5 (6.7) |
| Non-albicans *Candida* spp. | 3 (4.0) |
| *Candida albicans* | 2 (2.7) |
| Total | 74 (100) |

MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*

**Table 2.** Prevalence and causative organisms of bacteremic febrile neutropenia from 2000(9) vs. 2010

| Year | 2000 n (%) | 2010 n (%) | *p*-value |
|---|---|---|---|
| Gram-negative bacteria | 54 (88.6) | 57 (77.0) | 0.588 |
| Gram-positive bacteria | 7 (11.4) | 12 (16.3) | 0.493 |
| ESBL-producing gram-negative bacteria | N/A | 17 (29.8) | N/A |
| MRSA | 0 (0.0) | 3 (25.0) | 0.203 |
| Fungus | 0 (0.0) | 5 (6.7) | 0.045 |
| Total | 61 (100) | 74 (100) | |

ESBL = extended-spectrum betalactamase; MRSA = methicillin-resistant *Staphylococcus aureus*

**Table 3.** Empiric antimicrobial treatment in patients with febrile neutropenia

| Antibiotic | Frequency of prescription, n (%) |
|---|---|
| Ceftazidime + amikacin | 201 (64.8) |
| Piperacillin/tazobactam | 38 (12.3) |
| Imipenem | 22 (7.1) |
| Meropenem | 21 (6.8) |
| Cefepime | 7 (2.3) |
| Ceftazidime + ciprofloxacin | 4 (1.3) |
| Cefepime + amikacin | 1 (0.3) |
| Add vancomycin | 9 (2.9) |

**Table 4.** Percentage of susceptible Gram-negative organisms to antimicrobial agents

| Antibiotic | % coverage: Gram-negative bacteria |
|---|---|
| Ceftazidime | 74.1 |
| Cefepime | 74.1 |
| Piperacillin/tazobactam | 87.5 |
| Imipenem | 92.9 |
| Meropenem | 91.1 |
| Ceftazidime or ciprofloxacin | 82.1 |
| Ceftazidime or amikacin | 89.3 |
| Cefepime or amikacin | 89.3 |

plus amikacin provided coverage of 89.3%. Chemotherapy regimens in this study consisted of idarubicin plus cytarabine (22.6%), high dose intermittent cytarabine [HiDAC] (16.1%), hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [hyper-CVAD] (8.4%), and cyclo-

**Table 5.** Factors associated with treatment outcomes in febrile neutropenic patients

| Factors | Outcome | | *p*-value |
|---|---|---|---|
| | Unfavorable (n = 176), n (%) | Favorable (n = 134), n (%) | |
| Male gender | 67 | 38 | 0.220 |
| Age (year), mean ± SD | 47.3±15.4 | 45.5±17.5 | 0.410 |
| BMI <20 kg/m$^2$ | 54 | 41 | 0.890 |
| Hematologic malignancy | | | <0.001 |
| Acute leukemia | 83 | 24 | |
| Lymphoma | 43 | 29 | |
| Others | 3 | 7 | |
| Solid malignancy | | | 0.078 |
| Breast cancer | 2 | 19 | |
| Others | 8 | 16 | |
| Uncontrolled cancer | 132 (75.0) | 77 (57.5) | 0.001 |
| First chemotherapy | 83 (47.4) | 38 (28.4) | 0.001 |
| Use of growth factor | 99 (56.6) | 84 (62.7) | 0.254 |
| Use of antibiotic prophylaxis | 30 (17.1) | 19 (14.2) | 0.734 |
| Duration of neutropenia ≥7 days | 32 (18.2) | 5 (3.7) | 0.002 |
| Onset of fever at presentation | | | 0.042 |
| ≤24 hours | 59 (33.5) | 33 (24.6) | |
| 24 to 48 hours | 39 (22.2) | 47 (35.1) | |
| >48 hours | 26 (14.8) | 22 (16.4) | |
| Fever (≥39°C) | 151 (85.8) | 67 (50.0) | <0.001 |
| SBP <90 mmHg | 43 (24.4) | 7 (5.2) | <0.001 |
| PR ≥120/minute | 68 (38.6) | 38 (28.3) | 0.059 |
| RR >24/minute | 18 (10.2) | 2 (1.5) | 0.002 |
| Respiratory failure | 25 (14.2) | 1 (0.7) | <0.001 |
| Need for inotropic drugs | 34 (19.3) | 6 (4.5) | <0.001 |
| Mucositis | 16 (9.1) | 17 (12.7) | 0.291 |
| Central venous catheter insertion | 17 (9.7) | 3 (2.2) | 0.008 |
| Underlying heart disease | 10 (5.7) | 11 (8.2) | 0.380 |
| DM | 6 (3.4) | 9 (6.7) | 0.179 |
| Previous febrile neutropenia | 63 (36.0) | 48 (35.4) | 0.996 |
| Hb <8 g/dl | 72 (41.1) | 41 (30.6) | 0.062 |
| ANC <100/mm$^3$ | 99 (56.6) | 71 (53.0) | 0.567 |
| ANC (mm$^3$), median (range) | 50 (0 to 1390) | 70 (0 to 1,000) | |
| Platelets <50,000/mm$^3$ | 45 (25.7) | 55 (41.0) | 0.004 |
| Platelets (mm$^3$), median (range) | 26,000 (1,000 to 247,000) | 32,500 (2,000 to 350,000) | |
| Cr ≥2 mg/dl | 11 (6.3) | 2 (1.5) | 0.041 |
| AST ≥80 U/L | 6 (3.4) | 2 (1.5) | 0.483 |
| ALT ≥74 U/L | 20 (11.4) | 13 (9.7) | 0.965 |
| ALP ≥117 U/L | 34 (19.4) | 20 (14.9) | 0.720 |
| TB ≥2 mg/dl | 17 (9.7) | 6 (4.5) | 0.171 |
| Albumin <2.5 mg/dl | 13 (7.4) | 6 (4.5) | 0.521 |

ANC = absolute neutrophil count; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; Cr = creatinine; DM = diabetes mellitus; Hb = hemoglobin; PR = pulse rate; RR = respiratory rate; SBP = systolic blood pressure; SD = standard deviation; TB = total bilirubin

phosphamide, hydroxydaunorubicin, vincristine, and prednisone [CHOP] regimen (6.8%). One hundred and ninety-nine patients (64.2%) had febrile neutropenia during the first course of chemotherapy, and 111 episodes (35.8%) developed in patients with previous febrile neutropenia.

**Table 6.** Factors associated with mortality in febrile neutropenic patients

| Factors | Outcome | | *p*-value |
|---|---|---|---|
| | Death (n = 61), n (%) | Survival (n = 249), n (%) | |
| Male gender | 29 | 76 | 0.101 |
| Age (year), mean±SD | 54.9±14.0 | 44.2±16.1 | <0.001 |
| BMI <20 kg/m$^2$ | 18 | 77 | 0.969 |
| Hematologic malignancy | | | 0.004 |
| Acute leukemia | 19 | 88 | |
| Lymphoma | 26 | 46 | |
| Others | 8 | 47 | |
| Solid malignancy | | | 0.023 |
| Breast cancer | 0 | 21 | |
| Others | 6 | 18 | |
| Uncontrolled cancer | 53 (86.8) | 156 (62.7) | <0.001 |
| First chemotherapy | 30 (49.2) | 91 (36.5) | 0.070 |
| Use of growth factor | 36 (63.9) | 147 (59.0) | 0.998 |
| Use of antibiotic prophylaxis | 8 (13.1) | 41 (16.5) | 0.755 |
| Duration of neutropenia >7 days | 10 (16.4) | 27 (10.8) | 0.156 |
| Onset of fever at presentation | | | 0.569 |
| ≤24 hours | 21 (34.4) | 171 (68.7) | |
| 24 to 48 hours | 15 (24.6) | 71 (28.5) | |
| >48 hours | 8 (13.1) | 40 (16.1) | |
| Temp (≥39°C) | 55 (90.2) | 163 (65.5) | <0.001 |
| SBP <90 mmHg | 37 (60.7) | 13 (5.2) | <0.001 |
| PR ≥120/minute | 34 (55.7) | 72 (28.9) | <0.001 |
| RR >24/minute | 16 (26.2) | 4 (1.6) | <0.001 |
| Respiratory failure | 25 (41.0) | 1 (0.4) | <0.001 |
| Need for inotropic drugs | 29 (47.5) | 11 (4.4) | <0.001 |
| Mucositis | 8 (13.1) | 25 (10.0) | 0.439 |
| Central venous catheter insertion | 16 (26.2) | 4 (1.6) | <0.001 |
| Underlying heart disease | 7 (11.5) | 14 (5.6) | 0.149 |
| DM | 5 (8.2) | 10 (4.0) | 0.185 |
| Previous febrile neutropenia | 18 (29.5) | 93 (37.3) | 0.252 |
| Hb <8 g/dl | 24 (39.3) | 89 (32.1) | 0.600 |
| ANC <100/mm$^3$ | 35 (57.4) | 135 (52.2) | 0.657 |
| ANC (mm$^3$), median (range) | 50 (0 to 820) | 69 (0 to 1,390) | |
| Platelets <50,000/mm$^3$ | 16 (26.2) | 84 (33.7) | 0.261 |
| Platelets (mm$^3$), median (range) | 27,500 (2,000 to 23,100) | 29,000 (1,000 to 350,000) | |
| Cr ≥2 mg/dl | 8 (13.1) | 5 (2.0) | 0.001 |
| AST ≥80 U/L | 4 (6.6) | 4 (1.6) | 0.071 |
| ALT ≥74 U/L | 13 (21.3) | 20 (8.0) | 0.008 |
| ALP ≥117 U/L | 17 (27.9) | 37 (14.9) | 0.060 |
| TB ≥2 mg/dl | 11 (18.0) | 12 (4.8) | 0.002 |
| Albumin <2.5 mg/dl | 11 (18.0) | 8 (3.2) | 0.001 |

ANC = absolute neutrophil count; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; Cr = creatinine; DM = diabetes mellitus; Hb = hemoglobin; PR = pulse rate; RR = respiratory rate; SBP = systolic blood pressure; SD = standard deviation; TB = total bilirubin

**Table 7.** Multivariate analysis for factors associated with clinical outcomes

| Clinical outcome | Factors | OR (95% CI) | *p*-value |
|---|---|---|---|
| Unfavorable outcome | Hematologic malignancy | 6.307 (2.088 to 19.052) | 0.001 |
| | Peak temperature ≥39°C | 6.063 (2.548 to 14.422) | <0.001 |
| | Hypotension | 4.123 (1.183 to 14.368) | 0.026 |
| Mortality | Age | 1.037 (1.003 to 1.073) | 0.033 |
| | Uncontrolled cancer | 5.430 (1.331 to 22.158) | 0.018 |
| | Peak temperature ≥39°C | 6.665 (1.553 to 28.598) | 0.011 |
| | Hypotension | 8.476 (2.728 to 26.336) | <0.001 |
| | Respiratory failure | 30.455 (2.628 to 352.879) | 0.006 |
| | ALT ≥74 U/L | 4.859 (1.508 to 15.657) | 0.008 |

ALT = alanine transaminase; OR = odds ratio

There were 134 episodes (43.2%) with favorable outcomes and 176 episodes (56.8%) with unfavorable outcomes and 32.6% of those required a change in antimicrobial treatment. Total mortality was 61 episodes (19.7%), and the most common cause of death was infection. Factors associated with treatment outcomes and mortality are shown in Table 5 and 6.

Several factors were found to be associated with treatment outcomes and mortality in univariate analysis, as shown in Table 5 and 6. These factors were included in multivariate analysis, as shown in Table 7. Factors independently associated with unfavorable treatment outcomes were hematologic malignancy ($p$ = 0.001), peak temperature of 39°C or higher ($p$<0.001), and hypotension ($p$ = 0.026). Factors associated with mortality were age ($p$ = 0.033), uncontrolled cancer ($p$ = 0.018), peak temperature of 39°C or higher ($p$ = 0.011), hypotension ($p$<0.001), respiratory failure ($p$ = 0.006), and increased ALT ($p$ = 0.008).

## Discussion

This study revealed acute leukemia, lymphoma, and other hematologic malignancies to be the major causes of febrile neutropenia, which is similar to the results of previous studies[7-10]. Studies from Western countries identified Gram-negative bacteria, especially Enterobacteriaceae, as the major causative organisms of febrile neutropenia, accounting for 60% to 70% of all infections. However, recent study reported Gram-positive bacteria as being the etiologic agents in 60% to 70% of febrile neutropenia[4]. This study found that the predominant causative agents in our febrile neutropenic patients were still Gram-negative bacteria, although the percentage decreased to 77% in 2010 from 88.6% in 2000. Other centers in Thailand found a prevalence of Gram-negative bacteria that ranged from 61.3% to 87.8% in febrile neutropenic patients[9-11]. The most common Gram-negative bacterial infections were Enterobacteriaceae, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. In our previous study in 2000, we demonstrated that febrile neutropenic patients were treated with ceftazidime plus amikacin, which were active to all isolated of gram negative bacteria, assuming that ESBL-producing gram-negative bacteria may not be the main problem. In this study, however, we found that the prevalence of ESBL-producing gram-negative bacteria was as high as 29.8%[9].

The prevalence of Gram-positive bacteria in our study was 16.3%, which compared to the 11.4% rate reported in a previous study[9]. These changes in etiologic agents may have resulted from an increase in central vascular catheter use. Fungal infection was found in 6.7% of cases as a primary infection. Infections caused by resistant organisms have also increased. These include ESBL-producing Gram-negative bacilli, which were found in 17 episodes (29.8%), and methicillin-resistant *Staphylococcus aureus* [MRSA], which was isolated in three episodes (25%).

Blood cultures were positive in 23.9% of cases in this study, which is similar to the results of our previous study and to other studies that reported positive culture rates of 22% to 32%[7,12,13]. The most commonly used empiric antibiotic therapy in febrile neutropenic patients was ceftazidime combined with amikacin, which was found to be effective against Gram-negative bacterial pathogens in 89.3% of cases. Therefore, this drug combination should still be considered an appropriate antibiotic for treating patients with febrile neutropenia. However, the increasing prevalence of ESBL-producing organisms found in this study is of concern, and carbapenems may be an option in certain patients. Gram-positive bacteria were found to be MRSA in 25% of cases, so vancomycin should be considered in high-risk groups, such as patients with central venous catheters and those with mucosal inflammation.

The mortality rate was 19.7% in this study, which is similar to rates reported in other studies[13,14]. Factors

associated with poor treatment response included hematologic malignancy, peak temperature of 39°C or higher, and hypotension. Factors associated with mortality in febrile neutropenic patients include advanced age, uncontrolled cancer, peak temperature of 39°C or higher, hypotension, respiratory failure, and increased ALT, which reflects more severe disease in patients that expired.

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 are often 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.

## Conclusion

Consistent with the 2000 study finding, Gram-negative bacteria are still the most common etiologic organisms in febrile neutropenic patients at Siriraj Hospital. However, we found an increase in the proportion of ESBL-producing Gram-negative bacteria and fungal pathogens. Thus, the most appropriate empiric antimicrobial regimen for treating febrile neutropenia should cover primarily Gram-negative bacteria in addition to observing the patients' clinical. If the patient does not respond to standard treatment, drug resistance organisms and the presence of fungus need to be investigated. Peak temperature of 39°C or higher, and hypotension were identified as significant predictors of unfavorable outcomes, including death. Ongoing and vigilant surveillance of changing and emerging organisms is essential for optimizing patient outcomes.

## What is already known on this topic?

From previous study conducted at our center, the most common causative pathogens identified from blood in patients with febrile neutropenia were Gram-negative bacilli.

## What this study adds?

The most common etiologic organisms identified in febrile neutropenic patients admitted to Siriraj Hospital are still Gram-negative bacteria. The prevalence of ESBL-producing Gram-negative bacteria and fungal pathogens has increased significantly since 2000. Thus, the most appropriate empiric antimicrobial for treating febrile neutropenia should cover primarily Gram-negative bacteria. Furthermore, drug resistance and the presence of fungus need to be investigated if the patient does not respond to standard treatment.


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## Potential conflicts of interest

The authors declare no conflict of interest.

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