Febrile Neutropenia in Cancer Patients; Microbiology and Clinical Outcome of Empirical Antimicrobial Therapy

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ABSTRACT

Neutropenia is the single most important predisposing factor to infection in the person with cancer. Patients with febrile neutropenia are at risk of life threatening sepsis, and therefore require immediate empirical antibiotic therapy. Infections in the neutropenic patients can be rapidly fatal if not managed properly. Appropriate and in time therapy is a key factor for the management of febrile neutropenic patients. The objective of this study was to identify pathogens that caused infection, their susceptibility patterns and to evaluate the impact of inappropriate therapy on the clinical outcome of the patient. Based on set criteria 580 potentially eligible patients were selected during the time period of 1/1/2010 to 1/6/2012. Then the data from these patients were reviewed in detail and 208 episodes of febrile neutropenia from 155 patients were selected to be included in the study. Total 272 microorganisms were isolated from 155 patients, including all febrile episodes caused by single and multiple organisms. Out of 272, 200 (73.5%) were gram negative and 59 (21.6%) were considered to be gram positive. Amongst gram negative bacteria, *E.coli* with the percentage of 21.6% remained a predominant organism and Enterococci with percentage of 7.3 % was most frequently seen bacteria from gram positive bacteria. Candida species were the most frequently isolated organism from fungal origin. Out of twelve, 4 were *Candida albicans*, 3 were *Candida tropicalis* and 1 was *Candida krusei*. Three criteria were defined to evaluate the empirical therapy of the febrile neutropenic patients. According to those criteria, 92 (44.23%) episodes were found to have inappropriate empirical antibiotic therapy. Bacterial isolates of 39 episodes were found to be resistant against the prescribed therapy, which is the 42.3% of the all episodes indentified with inappropriate therapy. 30 episodes 32.6% were found to have delay in the empirical therapy and for remaining 23 episodes 25.0%, no fungal therapy was

prescribed after continuous episode of febrile neutropenia for 7 days. To evaluate the effect of empirical therapy on the clinical outcome of the patient Bivariate and logistic regression was performed. All risk factors of increased length of stay, which were found significantly associated with increase in length of stay during bivariate analysis, were later used in regression model. Hematologic malignancy, inappropriate empirical therapy, vasopresser use, with odd ratios of 5.00, 6.049, 2.23 respectively were significantly associated with the dependent variable and then bivariate association between each predictor variable and mortality was conducted. In logistic regression inappropriate empirical therapy and vasopresser use, with odd ratios of 4.147, 8.953 respectively were significantly associated with the mortality. In summary, this study found that patients with neutropenia, were at increased risk of death and longer length of stay when exposed to inappropriate empirical therapy, it was also found that patients exposed to inappropriate therapy had longer time to respond to the therapy which is then an important factor regarding the cost of treatment.

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LIST OF ABREVATIONS AND SYMBOLS

E. coli	= *Escherichia coli*
P. aeruginosa	= *Pseudomonas aeruginosa*
FN	=febrile neutropenia
ANC	= absolute neutrophil count
cells/mm^3	= cells per cubic millimeter
$	= US dollar
IDSA	= Infectious Diseases Society of America
ESBL	= extended-spectrum β-lactamase
NCCN	= National Comprehensive Cancer Network
AGIHO	= Infectious Diseases Working Party Germany
EORTC	= European Organization for Research on Treatment of Cancer
OR	=odds ratio
CI	= confidence interval
IV	= intravenous
S. aureus	= *Staphylococcus aureus*
spp	= species
AmB	= Amphotericin B deoxycholate
LOS	= length of stay

MRSA	= Methicillin-resistant *Staphylococcus aureus*
CBC	= complete blood count
UTI	= urinary tract infection
AKI	= acute kidney injury

Chapter 1

Introduction

1.1 Background and Rationale

Neutropenia is the single most important predisposing factor to infection in the person with cancer. Infection is the most common cause of death in the cancer patients. Weissv RV *et al.* (2003) conducted a retrospective study in 7 large states of America. They found that among 537,606 patients, infection and neutropenia were identified in 2,060,749 and 54,439 cases, respectively.[1] Studies have also reported that 48% to 60% of patients admitted with febrile neutropenia have infections.[2] These infections can be life threatening and increase both the morbidity and mortality.[3-6]

Patients with febrile neutropenia are at risk of life threatening infection, and therefore require immediate empirical antibiotic therapy. Infections in the neutropenic patients can be rapidly fatal if not managed properly. Appropriate and in time therapy is a key factor for the management of febrile neutropenic patients.

There was a study performed at the Songklanagarind hospital from May 2001 to July 2003, to determine treatment outcome using ceftazidime plus aminoglycosides in febrile neutropenic children with cancer. The authors conducted a prospective cohort study in 216 episodes of febrile neutropenia. Early and complete responses to antibiotics were identified in 108/216 (50.0%) and 133/216 (61.6%) episodes, respectively.[7] According to another study, response to empiric antimicrobial therapy was seen in 50% of febrile neutropenic patients. In the remaining 50%, second line and third line therapy was continued without any further change in 9 and 3 patients, respectively.[8] Hence, this showed that in the era of modern broad spectrum antibiotics, only about 50% of febrile neutropenic patients responded to empirical therapy. Efforts should be done to improve the appropriateness of the empirical therapy or to find the other factors which can influence the response of empirical therapy or patient's clinical outcome.

Selection of appropriate empirical therapy for febrile neutropenic patients is a key factor for a good clinical outcome of these patients. Patterns of infection and bacterial resistance may vary time to time and institution to institution. The choice of which antibiotic(s) to use needed to be established as a local policy, in consultation with the clinical teams managing patients on chemotherapy, and in accordance with local patterns of infection and bacterial resistance.

Over the past decade there has been a considerable change in the spectrum and antibiotic susceptibility patterns of bacteria causing infections in febrile neutropenic patients. During the 1960s and 1970s, gram negative bacteria predominated. Then, during the 1980s and 1990s, gram positive bacteria became was more common.[9] Currently, Enterobacteriaciae (e.g., *Enterobacter* spp. *Escherichia coli* & *Klebsiella* spp.) and coagulase negative Staphylococcus are the most common blood isolates in most centers. [6,10]

Use of broad spectrum antibiotics has resulted in emergence of multi drug resistant gram negative and gram positive bacteria. In recent years, some hospitals have experienced an increase of infections caused by multi drug resistant gram negative bacilli (such as *Acinetobacter* spp. or *Stenotrophomonas maltophilia*) and glycopeptides resistant gram positive cocci. Resistance among *Pseudomonas aeruginosa* is also an increasing concern. Historically, inadequately treatment of *P. aeruginosa* bacteremia in febrile neutropenic patients was associated with high mortality rate.[11] Surveillance studies done by the SENTRY program showed that 218 of a total 6,631 *P. aeruginosa* isolates recovered worldwide during 1997–1999, were multidrug-resistant. Extended-spectrum β-lactamase (ESBL) producing bacteria have also become a serious problem in some regions of the world.[12] In Asia, significant numbers of resistant isolates retrieved from febrile neutropenic patients have been reported in Malaysia[13], Taiwan[14], Korea[15] and Thailand.[52,32]Therefore detection of epidemiological and resistance patterns shifts requires frequent monitoring and surveillance. Particularly, at centers treating large numbers of patients, where institutional differences can be substantial. Up to date knowledge regarding the recent trends of bacteria causing infection in neutropenic patients and their resistance patterns is very necessary for the selection of appropriate empirical therapy, and to increase the response rate to empirical therapy in our institution.

Other than that, it would also be interesting and beneficial to know the percentage of patients has been treated with appropriate or inappropriate therapy and to what extent it can affect the ultimate outcome of the febrile neutropenic patients.

1.2 Research Questions

1. What are the recent trends in bacterial spectrum in FN patients admitted in Songklanagarind hospital?
2. What are susceptibility patterns of pathogens in adult febrile neutropenic patients during study time period?
3. How many patients treated with appropriate empirical antibiotic therapy?
4. What is the effect of inappropriate therapy on patient clinical outcome?

1.3 Objectives

1. To identify bacterial pathogens or fungus that caused infections in febrile neutropenic patients.
2. To assess the in vitro susceptibility patterns of bacterial pathogens isolated from febrile neutropenic patients.
3. To evaluate impact of inappropriate empirical therapy on clinical outcome of infections in febrile neutropenic patients.
4. To identify the risk factors for the mortality of the febrile neutropenic patients.

Chapter 2

Literature review

2.1. Definition

- **Neutropenia**
  - Neutropenia is defi ned as an absolute neutrophil count (ANC) of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 hour.[16]
- **Fever**
  - Fever is defined as a single oral temperature measurement of ≥38.3^{o}C (101^{o}F) or a temperature of ≥38.0^{o}C (100.4^{o}F) sustained over a 1-hour period.[16]

2.2 Consequences and significance of febrile neutropenia (FN)

Fever without the clinical signs of infections is the majority of clinical presentation of infection in patients with neutropenia and is frequently considered a medical crisis.[17] The frequency of neutropenia hospitalizations is predicted to be 60,000 cases per year in the United states. These hospitalizations are related with a towering mortality rate. Research studies approximate the death rate to be 6.8% and the rate climbs up to 10% for patients with a hematologic malignancy.[18]

Febrile neutropenia also has significant financial consequences.[18] Hospitalization for FN changes by cancer type with reference to length of stay and cost.[19-20] Data from a study including adult patients with cancer admitted with FN between 1995 and 2000 at 115 academic medical centers proposed that length of stay was longer in patients with leukemia than in those patients with lymphoma or solid tumors (19.7 days vs. 10.7 days vs. 8.13 days, respectively). The mean cost for leukemia patients were significantly higher than for lymphoma or solid tumors patients. [19]

Almost 60% of febrile episodes in neutropenic patient are related with no other signs and symptoms and are considered fevers of unidentified origin. Since about 70% respond to antibiotic treatment, it is likely that many of them had undetected infections.[21] For example,

pneumonia has been found at autopsy assessment in neutropenic patients who had a normal chest at examination. Sickle et al., (1997) established the lack of classic manifestations of infections in clinical studies of neutropenic patients.[21] They found that among patients with pneumonia, 84% of those with an adequate neutrophil count (ANC >1000/mm^3) produced purulent sputum compared to only 8% of those with severe neutropenia (ANC <100/mm^3). In patients with urinary tract infections, pyuria was noticed in 97% and 11% in patients with adequate neutrophil count and severe neutropenia, correspondingly. In a study of gram negative bacterial pneumonia in cancer patients, 38% of those with neutropenia (ANC <1000/mm^3) had a normal chest roentgenogram at the onset of their infections, although many developed abnormalities subsequently.[22] Because of these reasons, practitioner assessment of the causes of fever in neutropenic patients can be incorrect. In one study, physicians had to decide whether or not patients were infected based on their early evaluation and these evaluations were compared to the ultimate diagnosis.[23]The initial assessments were incorrect in 33% of the febrile episodes. Twenty eight percent of patients who had eventually proven to be infected were initially considered to have a fever of unidentified origin.

It is very vital to begin antibiotic therapy promptly when neutropenic patients develop fever because the infection may get worst rapidly if not treated. In a study of children with cancer who developed pneumonia, associated bacteremia was found in none of those with satisfactory neutrophil counts, but in 64% of those with neutropenia.[24] Most of bacteremic episodes caused by α-hemolytic streptococci responded immediately to antibiotic therapy even in patients with severe neutropenia. In recent years, however, some strains of several species have caused fulminant infection resulting in acute respiratory distress syndrome, septic shock or renal failure.[25]

2.3 Etiological pathogens

The bacterial etiology is often unidentified at the onset of infection. Awareness of the prevalence of causative bacteria in neutropenic patients with fever is important since timely adequate antimicrobial therapy is of vital importance. The epidemiology of bacteremia in neutropenic cancer patients has changed.[26] Published studies by the International Antimicrobial

Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (IATCG-EORTC) and other studies have demonstrated the changing epidemiology over the past 3 decades. Gram negative bacteria (GNB) caused approximately 70% of monomicrobial bacteremia in the 1970s, but the situation was entirely overturned by the late 1980s and 1990s, with gram positive organisms causing approximately 70% of the episodes.[27-30] The emergence of *coagulase-negative staphylococci* (CoNS), *viridans streptococci* and *enterococci* were primarily responsible for this change.[31] However, recent studies showed that trend is again changing to gram negative organism. Several studies were indicating change in prevalence of pathogens in different countries including Thailand. A five year review from 2004 to 2009 conducted at the department of medicine, Mahidol University; Ramathibodi Hospital showed total 70 febrile neutropenic patients that developed bacteremia. From those 70 patients, 92 episodes of bacteremia were observed. Gram negative bacteria remained the major organism causing bacteremia (73/102, 71.6%), followed by gram positive cocci (GPC) (24/102, 23.5%) and gram positive bacilli (5/102, 4.9%). Poly-microbial bacteremia occurred in 6 (6.5%) episodes. Among the GPC, *coagulase negative staphylococci* were the predominant pathogens (10/102, 9.8 %), followed by *Enterococcus* spp. (2/102, 2.0%). Mortality rate was 48.6 %. From univariate analysis, factors associated with death were, admission in intensive care unit ($p<0.001$), age >60 year old ($p<0.006$). There was no significantly difference in mortality rate among type of organism isolated.[32] Recent IDSA guideline for febrile neutropenia, released in 2010 also indicates about this change in prevalence of pathogens in febrile neutropenic patients, based on different studies. The most recent and important study was published in 2008 and conducted in an institute in Italy. Fever developed in 364 neutropenic patients (364/823 44.2%) and an infection was documented in 187 out of these 364 patients (22.7%), either clinically (6.1%) or microbiologically (16.6%). Among 164 pathogens isolated, gram negative (49.4%) outweighed gram positive bacteria (40.9%). *E. coli* being most frequent isolated organisms (23.2%). Another study showed similar results but, that study was conducted in hematopoietic stem cell transplant recipients.[16]

Fungal infections were first recognized many years ago as potential causes of persistent or recurrent fever in patients taking antibacterial agents during an episode of neutropenia. Fungi

are major pathogens, especially in patients with prolonged neutropenia who receive protracted courses of antibacterial agents. The predominant fungal pathogens are *Candida* species, *Aspergillus* species, *Cryptococcus neoformans*, and the *Phycomycetes. Candida* species are colonizers of human mucosal surfaces, they may cause bloodstream infection with mucosal barrier breakdown.[33-34] Invasive mold infections, including aspergillosis (the most common invasive mold infection), zygomycosis, and fusariosis, occur almost exclusively in high-risk patients with profound neutropenia (<100 cells/mm^3) lasting longer than 10-15 days. Patients at greatest risk are those treated for acute myelogenous leukemia, for which the incidence of invasive mold infection is 20 times greater than that seen among patients with lymphoma and multiple myeloma.[35] Following table, summarize few studies in which authors have found gram-negative bacteria as a leading cause in febrile neutropenic patients.

Table 1: Etiological pathogens isolated from patients with febrile neutropenia. [36-38]

Citation	**Total organisms/episodes**	**Gram negative bacteria**	**Gram positive bacteria**	**The most common organisms**
Zahid KF. et al. 2009	151	57.6%	42.3%	*E. coli* (23.1%) *P. aeruginosa* (12.5%)
Sigurdardottir K. et al. 2005	282	41%	40%	*E. coli* (25.6%) α- and non-haemolytic *streptococci* (15.6%)
Roongpoovapatr P. et al. 2010	84	63.9%	29.9%	*E. coli* (46.8%)

2.4. Treatment

2.4.1 Empirical therapy

The foremost complication of febrile neutropenia is septic shock and management is directed at preventing the development of this complication. Early detection of septic shock is vital to patient survival.

The use of combination regimen has been broadly adopted as they have synergistic effect and provide broad spectrum coverage against wide range of bacteria. This is very important in case of empirical therapy because physician don't know the actual pathogen at the time of staring therapy. Combination empirical antibiotic regimen may utilize a variety of antibiotics, usually this can be broken down in to three categories.

- Antipesudomonal beta-lactam plus an aminoglycosides.
- Antipesudomonal beta-lactam plus 2nd beta-lactam.
- Antipesudomonal beta-lactam plus an aminoglycocides and a glycopeptide.

The combination of an antipesudomonal peninicillin, cephalosporin or carbapenem and an aminoglycoside is one of the most commonly used empirical treatment regimens for the management of febrile neutropenia. Several practice guidelines for the management of febrile neutropenia e.g. IDSA, NCCN, AGIHO do not recommend to use combination therapy with aminoglycosides in all patients. It is recommended to use aminoglycosides in combination if patient was found in high suspicion (i.e. local epidemiology) of resistant gram negative infections, including *P. aeruginosa*, and if the patient is having severe sepsis and septic shock. Moreover, results from number of meta-analysis showed no benefit of combination therapy over single agent.[16]

Various options for intravenous antibiotics are existed, but these antibiotics are not without toxicity. Studies conducted by the European Organization for Research on Treatment of Cancer (EORTC) have provided particularly convincing evidence of the benefits of a long course of this therapy (combination of beta lactam drugs and aminoglycosides). The fourth EORTC trial compared short (3 days) vs. long (9 days) courses of therapy with an

aminoglycoside plus ceftazidime in 872 patients with granulocytopenia. Among 129 evaluable patients with gram-negative bacteremia associated with a single organism, the response rate was 81% in the long-course treatment group, compared with only 48% in the short-course group.[39] However, combination of beta-lactams and aminoglycosides was more likely to cause adverse effects e.g. nephrotoxicity, ototoxicity and hypokalemia.

Amphotericin B has been the standard empirical choice for fungal empirical therapy over 3 decades. However, a number of trials have identified roles for other antifungal agents, including itraconazole, voriconazole, and caspofungin. According to IDSA guideline, preemptive antifungal therapy is accepted as an alternative to empirical fungal therapy, but the quality and strength of evidence is weak as compared to the recommendation of starting empirical antifungal therapy after 7 days of continuous febrile neutropenia with wide spectrum antibacterial agents. Furthermore, percentage of patients with continuous neutropenic fever estimated to have IFI is high ranging from 15-45%. Delay of antifungal therapy to definitive diagnosis can easily provoke disseminated infection. One recent study published in 2011 indicated that empirical antifungal treatment decreased the incidence of invasive fungal disease and of attributable mortality with respect to a preemptive antifungal approach in neutropenic febrile patients with hematologic malignancies. Three hundred and ninety seven adults with hematologic malignancies included. A hundred and ninety patients had been treated with empirical antifungal therapy and 207 with preemptive antifungal therapy. There was a significantly lower incidence of proven/probable invasive fungal diseases in patients treated with empirical antifungal therapy (n=14, 7.4%) than in patients treated with preemptive therapy (n=49, 23.7%) ($P<0.001$). The rate of deaths attributable to invasive fungal diseases was significantly lower in subjects treated with empirical antifungal therapy (1 case; 7.1%) than in subjects treated with pre-emptive therapy (11 cases; 22.5%) (P=0.002). [40] In another study, preemptive treatment increased the incidence of invasive fungal disease, without increasing mortality. Twelve of 73 patients in the preemptive treatment group vs. 3 of 78 patients in the empirical treatment group were infected during induction therapy ($P < .01$) [41]. A meta - analysis conducted in 2008 showed that, empirical antifungal treatment is associated with a lower rate of IFIs but no significant difference in overall mortality.[42]

2.4.2 Documented therapy

Once having positive culture results, empirical therapy should be changed accordingly and should be more focused to the specific organism and site of infection. Susceptibility report should be given prime importance while selecting antibiotic for the patient. According to recent IDSA guidelines, vancomycin (or other agents active against aerobic gram positive cocci) is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia, but these agents can be used after having positive culture results.[16]

2.5. Outcome of inappropriate therapy

Inappropriate antibiotic therapy can affect patient outcome negatively. It can lead to negative clinical and economical outcomes such as increase length of stay in hospital, increase economic burden and mortality. In one such study, authors tried to evaluate the therapy, according to the time of administration and bacterial prevalence. They performed a retrospective cohort study of patients with monomicrobial bloodstream infection at a large urban hospital in the United States from 2001 to 2006. Impact of delay of active antimicrobial therapy on mortality was assessed by using multivariable logistic regression modeling with and without propensity score methodology. They evaluated 1,523 episodes of monomicrobial bacterial bloodstream infections at their institution. Nine hundred eighty three bacteremic episodes (64.5%) were treated with an active antimicrobial agent within 24 h of the index blood culture; the remaining 540 episodes (35.5%) were considered to have delay of active antimicrobial therapy. In adjusted analysis, among patients in the non-intensive care unit setting with an ANC of <100 cells/mm^3, delay therapy was associated with increased mortality (odds ratio [OR], 18.0; 95% confidence interval [CI], 2.84 -114.5; $P < 0.01$). Among intensive care unit patients with an ANC of <100 cells/mm^3, the effect of delay of active antimicrobial therapy on mortality was nearly significant (OR, 5.56; 95% CI, 0.85 to 36.3; $P = 0.07$). However, for patients who were non-neutropenic (ANC, >500 cells/mm^3) or had ANC of 100 to 500 cells/mm^3, delay of active antimicrobial therapy was not associated with increased mortality. While the delay of active antimicrobial therapy was not significantly associated with higher mortality for most patients in this cohort, patients with severe neutropenia appeared to be vulnerable.[43] For bacteremic patients without severe neutropenia,

delay of active antimicrobial therapy did not appear to significantly impact mortality. Although it is reasonable to expect inadequate antimicrobial therapy to worsen mortality, this relationship is complex and not consistently supported in the literature. While several studies have shown an association between inappropriate antimicrobial therapy and mortality, other studies have not found a significant association.

A single centre retrospective analysis of the outcome of febrile neutropenia treated with broad-spectrum combination antibiotics was done. A total of 120 episodes of fever occurred in 78 patients. All patients were suffering from various hematological disorders on conventional treatment or receiving peripheral blood stem cell transplantation. Each episode of febrile neutropenia was treated with IV ceftriaxone and amikacin as first line therapy. If there was no response in 48 hours or if patients deteriorated clinically, subsequent changes were made until fever settled or neutrophils recovered. Response to empiric therapy was seen in 50%. In the remaining 50%, second line and third line therapy was continued without any further change in 9 and 3 patients respectively. Imipenem was used in combination with amikacin as salvage therapy as a last resort in 40 patients who failed to respond to various combinations of antibacterial agents. Out of these 40 patients, 10 developed fungal infections and could not survive while the remaining 30 defervesce within 72 hours of starting this combination. In 120 episodes of febrile neutropenia, 78 patients were on chemotherapy or pre or post bone marrow transplantation and *E. coli, S. aureus, Klebsiella* spp., *Candida* spp., and *P. aeruginosa,* were the most common organisms isolated.[8] Traditionally, broad-spectrum antibiotic combination is used as empirical therapy in febrile neutropenia. Different studies reports that a high percentage of patients require modification in therapy due to inappropriate response. Inappropriate therapy leads to modification in therapy later, or leading to salvage therapy like is in the study given above, [8] treatment outcome was classified as a success without modification when patient recovered from fever and neutropenia on initial empirical therapy. Success with modification involved ultimate recovery from fever and neutropenia but requiring alteration different antibiotic, antifungal or antiviral agent. The treatment was considered as failure if fever persisted for longer than 7 days without any response leading to patients′ death or the patient showed clinical deterioration with or without persistence of primary isolated microorganism or detection of a new organism. So according to their criteria more than 40

patients can be considered as treatment failure. This is the point which we need to focus, how can we increase the response rate to empirical therapy in our institution. One of the reasons to low response to empirical therapy can be inappropriate therapy as indicated in this study. *E. coli*, *Klebsiella* species and *P. aeruginosa* were the most common gram negative isolate while *Staphylococcus aureus* was the most common gram positive organism isolated. Bacterial pathogens were found to be susceptible to these following four drugs including imipenem, cefepime, piperacillin-tazobactam and amikacin. While they were highly resistant to other 3rd generation cephalosporin, aminoglycosides and quinolones. Ceftriaxone was chosen as first line therapy which later found to be ineffective due to high resistance level of bacteria to this drug in their institution.

There are some other important aspects about empirical therapy for febrile neutropenic patients which we should consider. One of them is economical effect and length of stay in hospital. Basically, increased cost of treatment is proportional to length of stay in hospital. Some studies tried to find out differences in response rates, but one study tried to find out the differences response time and cost of febrile neutropenia treatment for the regimens which has similar response rate. These differences should be given equal importance as we know that increase length of stay increase the chances of nosocomial infections. So, this is another parameter which we can use to select the most appropriate therapy for our patients. Considering regimens with late response as inappropriate regimens would play role in the good clinical outcome and cost effectiveness of the treatment. Data from 488 episodes of febrile neutropenia, treated with either of two commonly used antibiotics imipenem and ceftazidime during six clinical trials, were pooled to compare the median time to clinical response, days of antibiotic therapy and hospitalization, and estimated costs. Response rates were similar; however, the median time to clinical response was significantly shorter with imipenem based regimens (5 days) compared with ceftazidime based regimens (7 days; $P = .003$). After 72 hours of therapy, 33% of patients who received imipenem based regimens but only 18% of those who received ceftazidime based regimens had responded ($P = .01$). These differences resulted in fewer days of antibiotic therapy and hospitalization with imipenem based regimens (7 and 9 days) compared with ceftazidime based regimens (9 and 12 days, respectively; $P < .04$) and in significantly lower estimated median costs ($8,491 v $11,133 per episode; $P =$

.03). Early discharge at the time of clinical response should reduce the median cost from $10,752 to $8,162 ($P < .001$).[44]

An important study conducted by the European Organization for Research and Treatment of Cancer International Antimicrobial Therapy Cooperative Group, compared empirical AmB therapy with no antifungal therapy (the control group) in treating febrile neutropenic patients with cancer, 75% with leukemia. All patients received myelosuppressive treatment. In this study, antifungal therapy was introduced after 4 days of persistent fever. Outcome measurements were clinical response defined as success or failure in terms of the course of fever; documented invasive fungal infection; and mortality due to fungal infections. Response rates were 69% in the AmB group and 53% in the control group. There were 6 documented invasive fungal infections. Four out of 6 were considered to be severe, among the 64 patients in the control group, compared with only 1 among the 68 patients randomized to receive AmB ($P = .1$). Four patients (6%) in the control group died because of fungal infection, whereas there were no deaths attributable to fungal infection in the AmB group ($P = .05$).[45]

2.6. Risk factors influencing outcome

Febrile neutropenia is a widespread complication of therapy among patients with cancer. In recent years, numerous studies have looked risk factors for bad outcomes and mortality in patients with cancer, and tried to stratify patients with febrile neutropenia into risk categories to investigate various therapeutic strategies. When we are trying to find out the effect of empirical therapy on the clinical outcome of the patient, it is very important to consider the other risk factors which can possibly affect the clinical outcome of the patients. Despite the widespread approach of treating all febrile neutropenic patients with empiric broad spectrum antibiotics for potential bacteremia, febrile neutropenia in some age groups of patients with cancer remains associated with a significant mortality rate. This tells us that certain host or disease related factors may influence mortality resulting from febrile neutropenia. Basu SK. et al., (2005) conducted a retrospective study. The aim of this study was to evaluate risk factors for longer length of stay (LOS) and mortality among hospitalized children with cancer who has

febrile neutropenia. A total of 12,446 patients were identified for the study. The LOS was 5 days or less for 6,799 patients, and greater than 5 days for 5,647 patients. The mortality rate was 3%. On Bivariate analysis, race, age, cancer type, and associated complications (bacteremia/sepsis, hypotension, pneumonia, and fungal infections) were significantly associated with longer length of stay and death. On multivariate analysis, age group, race, cancer type, and the complication variables were significantly associated with increased risk of longer LOS and death. Certain types of cancer (Hodgkin's disease, osteosarcoma/Ewing's sarcoma, rhabdomyosarcoma, compared with acute lymphoblastic leukemia) and year of discharge after 1995 were significantly associated with a reduced risk of longer length of stay and/or mortality.[46] As anticipated, the complication diagnoses were considerably associated with both longer length of stay and death. An identification of sepsis or bacteremia conferred a 10-fold increase in the risk of death. Thus, despite the widespread use and availability of powerful antibiotics, bacteremia/ sepsis remains the most important independent prognostic marker for mortality. Pneumonia was associated with an eight-fold increase in the risk of death. Fungal infections were associated with a five-fold increase in the risk of death.

Lin MY et al., (2008) conducted a similar type of study. On bivariate analysis of covariates with mortality as outcome, they found that vasopresser use, ICU stay, severe and moderate neutropenia, receipt of antibacterial in prior 30 days, nosocomial infection, imipenem-resistant *P. aeruginosa*, significantly associated with mortality.[43] Several other studies given below (table 2) tried to find out the factors which can influence the clinical outcome of the febrile neutropenic patients. All these studies tried to find out variables or risk factors which can possibly affect the ultimate outcome of febrile neutropenic patients. Following factors were commonly identified in these studies, circulatory shock requiring vasopressors, respiratory failure, acute renal failure, bacteremia, neutropenia level (ANC,<100 cells/mm^3), types of organism (gram negative bacteria), pneumonia. Besides that gender (Male/Female) was also included to evaluate if gender influence the clinical outcome of the patients.

Table 2: Risk factors for hospital mortality and length of stay in febrile neutropenic patients. [19, 47-51]

Reference No.	Risk factors	Odd ratios (95% CI)
19	Gram-negative sepsis	4.92 (4.50-5.39)
	Invasive aspergillosis	3.48 (2.70-4.48)
	Invasive candidiasis	2.55 (1.94-3.34)
	Lung diseases	3.94 (3.64-4.26)
	Cerebrovascular disease	3.26 (2.64-4.02)
	Renal disease	3.16 (2.89-3.46)
	Liver disease	2.89 (2.48-3.37)
	Pneumonia	2.23 (2.04-2.45)
	Gram-positive sepsis	2.29 (2.01-2.60)
	Hypotension	2.12 (1.85-2.42)
	Pulmonary embolism	1.94 (1.44-2.60)
	Leukemia	1.47 (1.34-1.61)
47	Metastases	2.28 (1.81 - 2.88)
	Hypotension	3.79 (2.55 - 5.62)
	Pneumonia	2.39 (1.90 - 3.01)
48	Severe sepsis	*HR 31.5 (3.5-286.4)

	Shock	*HR 38.0 (5.4-267.8)
49	Inappropriate initial antimicrobial Treatment	2.04 (1.42-2.92)
	Respiratory failure	5.18 (3.30-8.13)
	Circulatory shock	4.00 (2.71-5.91)
50	"Sick" clinical appearance	7.41 (3.50 -15.72)
	Relapse of malignancy	3.14 (1.36 -7.25)
	Underlying diagnosis of AML	3.15 (1.10-9.04)
51	Hematological malignancy	2.42 (0.47 - 12.5)
	Severe dehydration	3.92 (0.90 - 17.04)
	ER Creatinine ≥ 1mg/dl	2.38 (0.48 - 11.7)
	Positive blood culture	4.76 (1.09 - 20.9)
	Pneumonia on Chest X-ray	8.14 (1.81 - 36.7)
	Hb Level in Emergency/OPD <10 g/dl	2.16(0.53 - 8.78)

*Hazard ratio

2.7. Antibacterial resistant prevalence in Thailand

As we have already discussed that it is very important to know about the resistant prevalence of pathogens involved in infections of febrile neutropenia patients. Specifically, it would be beneficial to know about the resistant prevalence in other parts of Thailand. Unfortunately, data regarding this issue in Thailand is very limited in all well recognized primary literature sources.

One study to determine prevalence of antibiotic resistant bacteria was performed at department of medicine, Faculty of Medicine, Siriraj Hospital. There were 140 patients. Seventy five (53.6%) were females. The mean age was 49.3 years. The bacteria commonly recovered were *E. coli* (77.9%), *Klebsiella pneumoniae* (46.4%), *Enterobacter* spp. (20%) and *Enterococcus* spp. (45.7%). ESBL-producing gram negative bacteria, *P. aeruginosa*, *Acinetobacter* spp. and MRSA were found in 13.6%, 8.6%, 5% and 1.4%, respectively. The susceptibility rate of *E.coli*, *K. pneumoniae* and *Enterobacter* spp. to co-trimoxazole, co-amoxiclav and ciprofloxacin was 51.5%, 73.2% and 74.8% respectively. Less than 50% of ESBL-producing gram negative bacteria, *P. aeruginosa* and *Acinetobacter* spp. were susceptible to the aforementioned oral antibiotics.[52]

Another study conducted at Ramathibodi Hospital, Bangkok, Thailand. They retrospectively reviewed medical records among patients admitted with febrile neutropenia and bacteremia after chemotherapy for hematological malignancies from January 1, 2004 to March 31, 2009. Patients' clinical, microbiological data and outcome were analyzed. The overall rate of multi-drug resistant GNB (MDR-GNB) bacteremia was high (23/102, 22.5%). Extended spectrum beta-lactamase producing Enterobacteriaciae was the major type (15, 14.7%) of MDR-GNB. All resistant GPC remained sensitive to vancomycin.[32]

2.8. Study site Back Ground: (Songklanagarind hospital)

Songklanagarind hospital started services on February, 1982. It now has 853 patient beds, and provides medical service to in and out patients, accident and emergency patients in various fields. There is no specific ward for oncology patients

Chapter 3

Methodology

3.1 Study design

This was a retrospective cohort study. Data of the patients admitted to the Songklanagarind hospital from 1/1/2010 to 1/6/2012 was evaluated retrospectively.

3.2 Study population

Oncology patients, admitted to the Songklanagarind Hospital during study period from 1/1/2010 to 1/6/2012.

3.3 Sample size

- Software from OpeniEpi was used to calculate sample size.[53-54]
- Two-sided significance level(1-alpha):95%
- Power(1-beta, % chance of detecting):80 %
- Ratio of sample size, Unexposed/Exposed:1.5
- Percentages of exposed and unexposed patients were taken from previous studies.

Table 3: Sample size calculation.

Risk factors for LOS/Mortality	% of patients unexposed with outcome	% of patients exposed with outcome	Kelsey Sample size	Flesis with CC Sample size
Bacteremia	1.7	9.0	264	348
Hypotension	2.7	11.2	260	270
Pneumonia	2.2	15	137	177
Severe sepsis	1.3	42.9	29	38
Age >65	5.1	34.7	54	69
Solid/liquid tumor	6.4	14.2	464	534

3.4 Study sample

3.4.1 Inclusion criteria

Patients who were ≥ 18 years old and

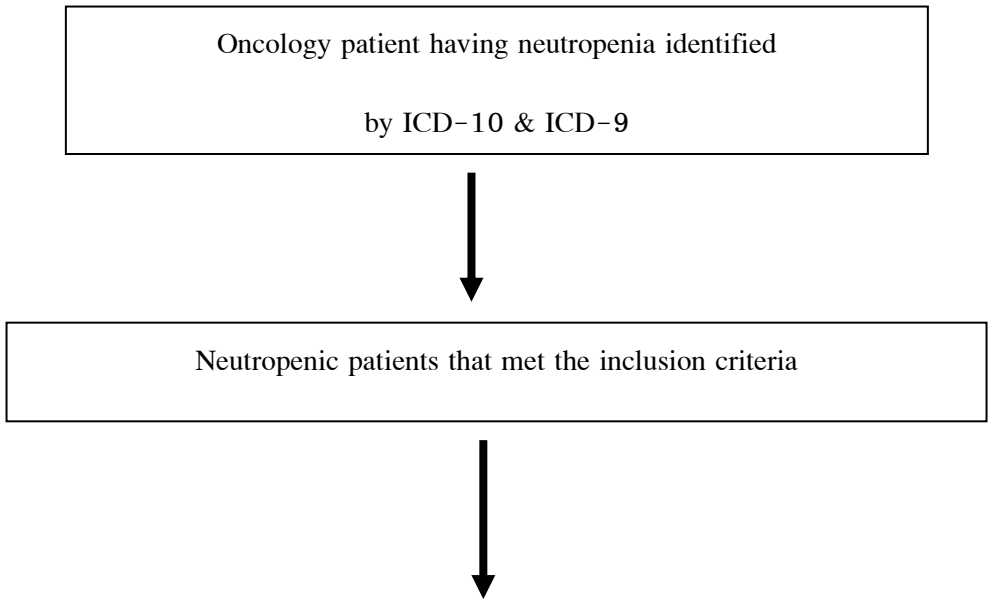
- Were diagnosed acute or chronic leukemia, lymphoma or solid tumors.
- Met criteria for febrile neutropenia (fever ≥38.3°C on one occasion or ≥38.0°C sustained for one hour and with an absolute neutrophil count of less than <500 cells / mm^3).
- Had positive culture results (bacteria/fungi).

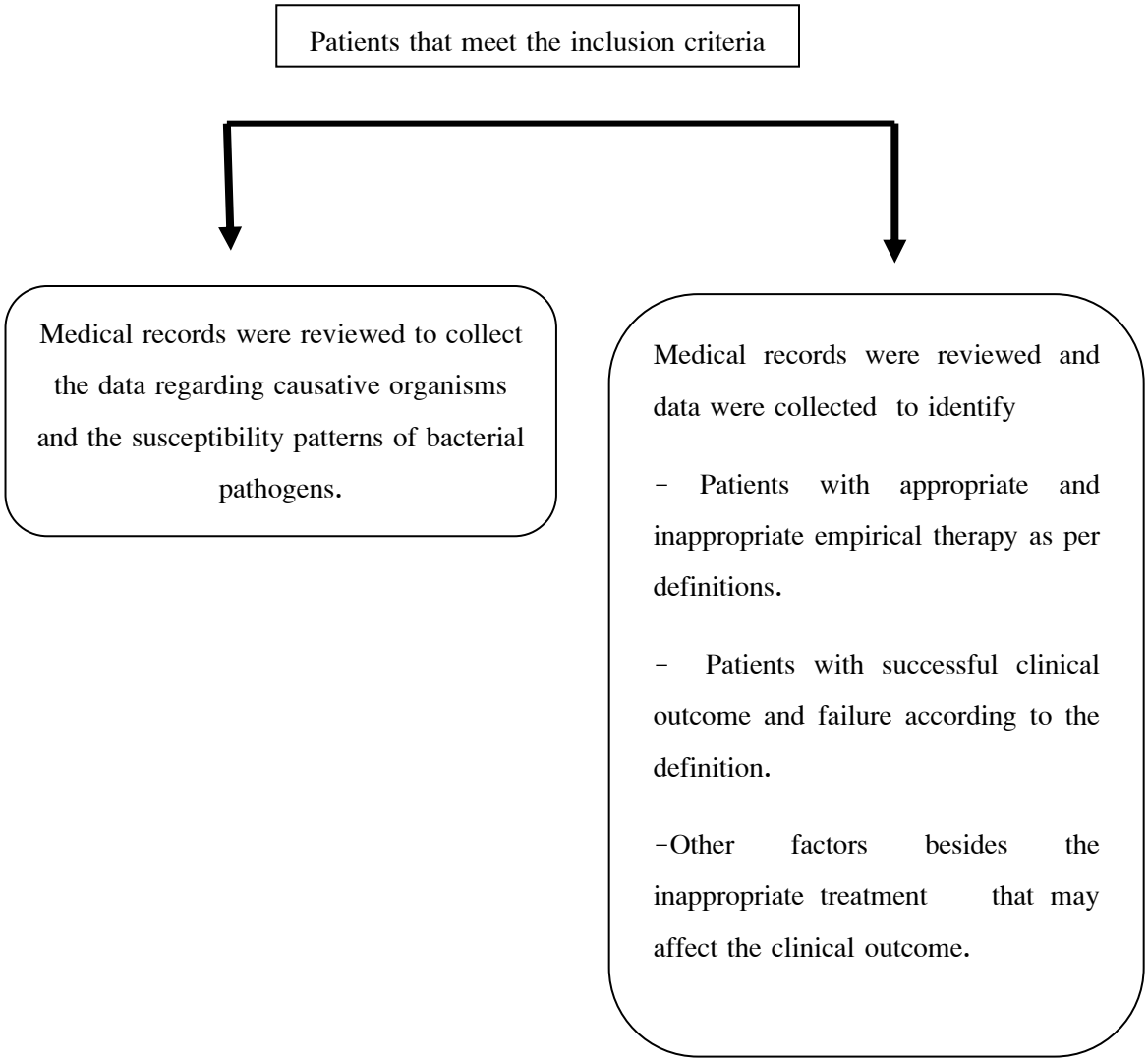
3.4.2 Exclusion criteria

- Patients with uncompleted medical records.
- Outpatients.

3.5 Data collection and analysis process

Figure-1: Flow chart for data collection process.





3.6 Identification of the patient

In Songklanagarind Hospital all patient data has available in electronic research database. All the diseases are classified by the ICD-10 & ICD-9 system. ICD-10 for Cancer patients was used to locate the HN of oncology patients. Data for all of these patients were then reviewed according to our inclusion criteria to select the sample population.

Demographics data of the patient was recorded, only the patients above 18 years of age were included in the study. Complete blood count (CBC) was used to identify the patient with neutropenia and time period of neutropenia was also recorded, temperature & microbiology data were then evaluated according to the time period of neutropenia for the respective patients. All different episodes of febrile neutropenia were included in the study from a single patient.

3.7 Clinical analysis

Microbiology

Microbiology Data of all the selected patients was reviewed to record the different organisms (bacterial/fungus) causing infection in patients and to find out the susceptibility or resistance patterns of those bacterial pathogens. Effect of length of stay on resistance patterns of organisms were evaluated taking mean of LOS (45days) as cut point, beside that effect of consecutive number of febrile episodes on resistance patterns was also evaluated.

Pharmacotherapy

The empirical antibiotics / antifungal regimens were evaluated and classified as appropriate and inappropriate therapy according to our definition. Clinical outcome of the infection in both arms was evaluated to find the effect of appropriate and inappropriate therapy.

Covariates/Risk factors

To compare patients on the basis of different covariates, some other data including renal status, respiratory status, vasopressor use and vital signs of the patients were collected.

3.8 Definitions

3.8.1 Successful outcome

Early response to initial antibiotics

Resolution of all the signs and symptoms of infection within 5 days of initial treatment was defined as good clinical outcome.

- Heart rate (less than 90 beats per minute)
- Respiratory rate (less than 20 breaths per minute)
- Temperature <36 °C (97 °F) or >38.3 °C (100 °F)

- **Pneumonia**
  - Resolution of other sign & symptoms related to pneumonia.

- **Skin and soft tissue infection**
  - Resolution of local sign and symptoms of skin and soft tissue infection.

- **Urinary tract infections (UTIs)**
  - Resolution of patient signs and symptoms of UTI.
    - Frequency / Urgency
    - Dysuria.
    - Suprapubic pain
  - Sterile urine cultures.

3.8.2 Poor outcome

- Persistent or deteriorated signs and symptoms of infection mentioned above after 5 days of initial therapy or change of initial antibiotic therapy was considered as poor outcome.

3.8.3 Mortality: Mortality due to any cause within 30 days of first episode of febrile neutropenia was also considered as poor outcome of treatment.

3.8.4 Length of hospital stay: Number of days, patient stayed in a hospital in single admission was considered as length of stay.

3.8.5 Inappropriate empirical therapy

- The bacterial isolate was not susceptible to the antimicrobial therapy.
- The antimicrobial was not clinically effective against the isolate.

- Dose is not appropriate according to the site and bacteria causing infection for example
  - Dose less than 1g every 12 hours of vancomycin for MRSA lung infection in patients with normal renal function and body weight or the through serum level less than 15 mg/L
  - Dose less than 15-20 mg/kg every 12 hours of vancomycin for meningitis or the through serum level less than 15 mg/L
- Antibiotics had not appropriate penetration to the site of infection.
  - Colistin given by IV route for meningitis
  - 1st and 2nd generation of cephalosporin for CNS infections except cefuroxime
  - Nitrofurantoin for prostatiis
  - Penicillin G, cephalexin, for prostatitis

- **Delay in antibiotic therapy**
  - Antibiotic administered after 24 hours of detection of temperature >38.3°C
- Delay in empirical therapy for fungus
  - antifungals had not been started after 4-7 days for febrile neutropenia with optimized bacterial therapy.

3.8.6 Positive culture

- Positive cultures from all the sterile sites was considered as true pathogens.
  - Hemoculture showing *S. epidermidis*, two different culture showing same organism was included.
- For culture from most common unsterile sites of infection, pathogen was considered as true pathogen according to the set criteria explained below.

Pneumonia

- Sample of sputum fall under this criteria for quality: Presence of <10 squamous epithelial cells (SEC) and >25 polymorphonuclear (PMN) cells

per low-power field (magnification, ×100), or ≥10 leukocytes for each SEC, will be regarded as being indicative of a high quality sample.

- All the samples declared of good quality by the physicians will be considered as good quality samples.
- Sample collected through endotracheal tube.

UTIs

- Bacteria identified at $\geq 10^5$ CFU/mL considered as a true bacterial pathogen.

Skin & Soft tissue infections

- Culture with needle aspiration and tissue culture were included in the study.
- Culture result from swab sample was not included in study.

3.8.7 Infection Diagnosis

- The diagnosis of hospital acquired pneumonia (HAP) was suspected if the patient had a radiographic infiltrate that was new or progressive, along with clinical findings suggesting infection, (new onset of fever, purulent sputum).
- All site specific infections were included in study, as diagnosed by the responsible practitioner.

3.9 Variable

Outcome variable

- Primary Outcome

  Mortality due to any cause within 30 days of first episode of febrile neutropenia was considered as poor outcome of treatment failure.

- Secondary Outcome

  Persistent or deteriorated signs and symptoms of infection mentioned above after 5 days of initial therapy or change of initial antibiotic therapy was considered as poor outcome.

- Length of hospital stay.

Independent Variable

- Circulatory shock requiring vasopressors
  - Systolic arterial pressure lower than 90 mm Hg
- Respiratory failure:
  - Mechanical ventilation applied by either an endotracheal tube or by mask.
- Acute renal failure
- Bacteremia
- Hospital length of stay
- Age
- Gender
- Neutropenia level (ANC, cells/L)
  - Severe neutropenia (<100)
  - Moderate neutropenia (100–500)
- Types of organism.(Gram + bacteria/ Gram – bacteria)
- Pneumonia

3.10 Data Extraction

- Patient demographics (Age, Sex , Weight)
- Medical history
  - Underlying disease
  - Previous episodes of febrile neutropenia
  - History of antibiotic use
- Vital signs

Laboratory report

- Absolute neutrophil count (ANC)
- Culture report
- Pathogen susceptibility results

- Complete blood count with differential leukocytes count
- Serum creatinine level
- Blood Urea nitrogen
- Type of disease (hematologic malignancy or solid tumor)

3.11 Data analysis

- Data analysis was done by spss 16.0 software.
- Descriptive analysis was done by calculating frequency and percentages.
  - Percentage of positive cultures.
  - Percentage of gram positive or gram negative pathogens isolated in these patients.
  - Percentages of specific microorganisms in gram positive and gram negative bacteria.
  - Percentage of fungal infections.
  - Susceptibility patterns of isolates to antimicrobial agents.
- Logistic regression was used to obtain the regression coefficient or estimate of the association between inappropriate therapy and clinical outcome, and to find out the effect of different risk factors on clinical outcome of the patients.
- Chi square test or Fisher exact was performed for bivariable analyses. (categorical variables) and t-test for continuous variables.

3.12 Validity and Reliability of study

3.12.1 Researcher training

- To evaluate the medical records in the local hospital

3.12.2 Consulting local experts

- Co-supervise in the project from hospital.

3.12.3 Translator:

- To help in the evaluation of medical records, and translate if Thai language is used.

3.13 Ethical Consideration

- Acquired an approval from the ethics committee of Faculty of Medicine, Prince of Songkla University.
- Privacy and Confidentiality:Use of patient number instead of their names.

3.14 Working plan

Activity	Months											
	1	2	3	4	5	6	7	8	9	10	11	12
Proposal defense												
Data collection												
Data analysis & interpretation												
Thesis writing & compilation												

Chapter 4

Results

Based on set criteria, 580 potentially eligible patients were selected during the time period of 1/1/2010 to 1/6/2012. Then, the data from these patients were reviewed in detail and 208 episodes of febrile neutropenia from 155 patients were selected to be included in this study. Other patients were excluded from the study due to incomplete medical records in 203 (35.0%) patients and undocumented infection in 222 (38.2%) patients.

Table 4: Characteristics of patients admitted with febrile neutropenia.

Characteristics	**All (*n*)**	***Appropriate* therapy(%)**	**Inappropriate therapy (%)**	***P value* (*n*) (chi-square)**
Number of episodes	208	97*	92	
Gender (Female)	208	63.9%	56.5%	0.299
Hematologic malignancy	208	39.1%	54.34%	0.057
Vasopresser Use	208	26.8%	39.13%	0.071
Severe Neutropenia <100 cells/ul	208	82.4%	90.21%	0.122
Bacteremia	208	62.88%	67.3%	0.072
Acute kidney injury	208	12.3%	20.6%	0.124
Respiratory failure	208	23.7%	40.21%	0.00

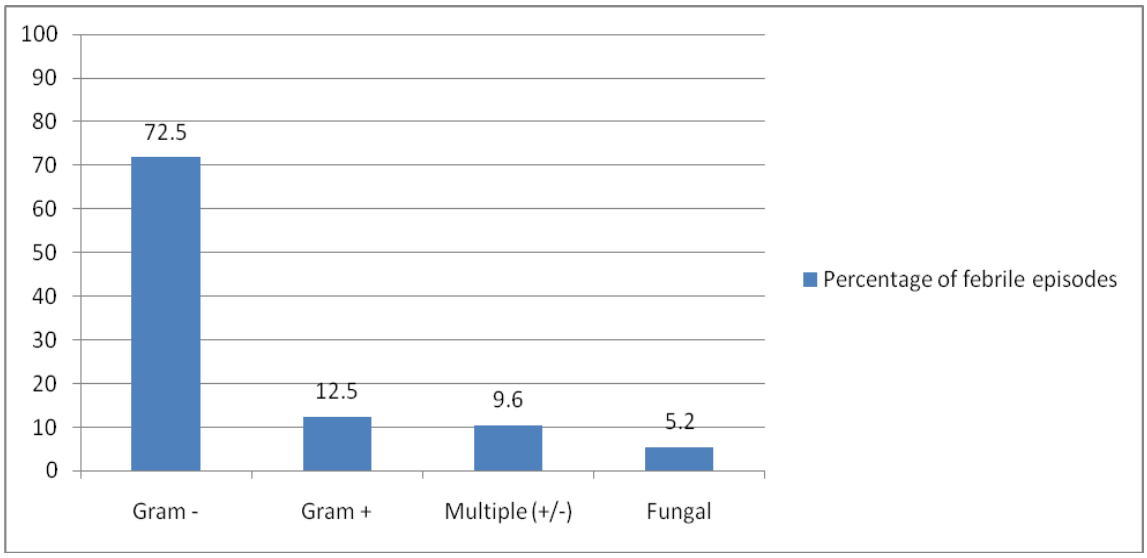
*Nineteen episodes were not classified as with appropriate or inappropriate therapy because of missing data.

The mean age of the final cohort was 46.2 with the range of (18-78) years.

4.1: Pathogens

According to the set criteria, all febrile neutropenic episodes included in this study had positive bacteriological or fungal cultures. Among 208 febrile neutropenic episodes, majority (151, 72.5%) were caused by gram negative microorganisms. Gram positive organisms were responsible for 26 episodes (12.5%). Twenty episodes (9.6%) were caused by multiple organisms including both gram positive & negative organisms. Eleven episodes (5.2%) were caused by organisms from fungal origin.

Figure-2: Percentages of febrile episodes according to different causative organisms.



Total 272 microorganisms were isolated from 155 patients, including all febrile neutropenic episodes caused by both single and multiple organisms. Out of 272, 200 (73.5%) were gram negative and 59 (21.6%) were gram positive bacteria. Amongst gram negative bacteria, *E.coli* with the percentage of 21.6% (59/272) was a predominant organism. Enterococci was most frequently seen (7.3 %, 20/272) among gram positive bacteria. Candida species were the most frequently isolated organism from fungal origin. Out of twelve, 4 were *Candida albicans*, 3 were *Candida tropicalis* and 1 was *Candida krusei*. Species of remaining 4 isolates of fungi were not identified. Frequencies of different individual microorganism are given below in the table-5.

Table-5: Organisms isolated from 208 episodes of febrile neutropenia. (n=272)

Microorganisms	No. of isolates	Percentage
Escherichia coli	59	21.6%
Klebsiella pneumoniae	53	19.4%
Pseudomonas aeruginosa	38	13.9%
Proteus mirabilis	13	4.7%
Enterococci species	20	7.3%
Streptococcus species	15	5.5%
Staphylococcus aureus	10	3.6%
Staphylococcus epidermidis	5	1.83%
Corynebacterium species	6	2.20%
Candida species	12	4.4%
Others*	41	15.07%

**Bacillus* species, *Acinetobacter baumanii*, *Enterobacter cloacae*, *Salmonella* species, *Aeromonas* species, *Morganella morganii*, *Proteus vulgaris*, *Sphingobacterium* species, *Haemophilus parainfluenzae*, *Stenotrophomonas maltophilia*.

4.2: Sites of Infection

One hundred and thirty nine (66.82%) out of 208 febrile neutropenic episodes were with bacteremia. Forty three (30.9%) out of 139 were with definite sources of infections. Among those with definite sources of infections, 17 (12.2%) were catheter related infections, 9 (6.4%) were gastrointestinal tract infections, 7 (5.0%) were Urinary tract infection, 7 (5.0%) were skin and soft tissue infections and 3 (2.1%) were lung infection. Sixty nine out

of 208 febrile neutropenic episodes (33.17%) were without bacteremia. Among those without bacteremia, urinary tract (40 episodes) with the percentage of 19.23% was the most common site of infection, followed by gastrointestinal tract (11 episodes), lung (10 episodes) and others (8 episodes) with the percentages of 5.28, 4.80 and 3.84, respectively.

Tabel-6: Identified sources of infection for febrile neutropenic episodes with bacteremia. (n=139)

Sites of infection	Number of episodes (%)
IV Catheter	17 (12.2%)
Gastro intestinal tract	9 (6.4%)
Urinary tract	7 (5.0%)
Skin and soft tissue	7 (5.0%)
Lungs	3 (2.1%)

Table-7: Site of infection for patients without bacteremia. (n=69)

Site of infection	Number (%)
Urinary tract	40 (19.23%)
Gastro intestinal tract	11 (5.28%)
Lungs	10 (4.80%)
Others	8 (3.84%)

4.3: Resistance patterns of isolated organisms

Resistance patterns of isolated organisms were also evaluated, during the study. *E.coli* and *K. pneumoniae* with the aggregate percentage of 41.1% (112) were the two most frequently isolated microorganisms. Out of total 112 isolates, 26 (23.2%) were found to be ESBL+. Imipenem and piperacillin/tazobactam were the most frequently used antibiotics and either of those were prescribed to all those 26 patients. Nine out of 26 isolates (34.6%) were resistant to piperacillin/tazobactam while only 2 (7.6%) were resistant to imipenem. To evaluate the effect of length of stay on the frequency of resistant organisms, mean of days from length of stay was taken (45days) and defined as cut point. Then frequencies of organisms

resistant to different antimicrobials during both time periods of length of stay, less than or equal to 45 days and more than 45 days were evaluated and found significant increase in the numbers of resistant organisms if the patients stayed longer than 45 days.

Table-8: Bivariate analysis of association between length of stay >45 days and antibacterial resistance in gram negative bacteria.

Anti-bacterial resistance	**Odd ratio**	**95% CI**	***P*-value**
Piperacillin/tazobactam	12.289	4.416-34.199	<0.05
Imipenem	4.232	1.457-12.288	<0.05
Meropenem	8.929	2.322-34.336	<0.05
Ceftazidime	8.750	3.505-21.843	<0.05

In bivariate analysis when we took consecutive episodes of febrile neutropenia as predictor, resistant to ceftazidime only with odd ratio of 2.460 (95% CI, 0.991-6.106) seem to increased from 1st febrile episode to the 2nd.

Table-9: Resistant patterns of gram negative organisms during different episodes of febrile neutropenia.

	Piperacillin/tazobactam		**Imipenem**		**Meropenem**		**Ceftazidime**	
	n	resistant	*n*	resistant	*n*	resistant	*n*	resistant
1st episode	114	11(9.6%)	122	5(4.0%)	114	5(4.3%)	114	22(19.2%)
2nd episode	27	4(14.8%)	28	3(10.7%)	27	2(7.4%)	27	10(37.0%)
3rd episode	13	6(46.5%)	15	6(40%)	11	3(27.2%)	11	6(54.5%)

Table-10: Resistance patterns of most frequently isolated gram negative bacteria.

Antibiotic	***E.coli***		***K. pneumoniae***		***P. aeruginosa***	
	n=59	*%*	*n=53*	*%*	*n=38*	*%*
Imipenem	1	1.69	1	1.88	9	23.68
Ertapenem	0	0	0	0	-	-
Meropenem	1	1.69	0	0	5	13.15
Piperacillin/tazobactam	2	3.38	13	24.5	3	7.89
Ceftazidime	15	25.42	16	30.1	1	2.63
Ceftriaxone	15	25.42	16	30.1	-	-
Amikacin	0	0	0	0	0	0
Ciprofloxacin	23	38.98	21	39.62	2	5.26
Gentamicin	9	15.25	9	16.98	1	2.63
Cotrimoxazole	27	45.76	23	43.39	-	-
Colistin	0	0	0	0	0	0

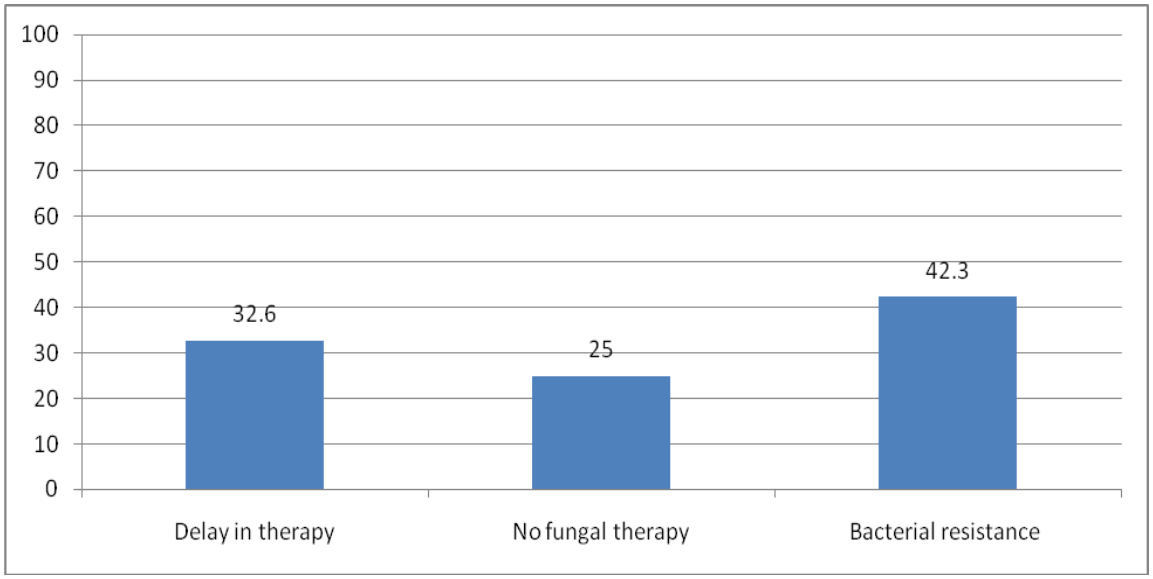
Among the gram positive bacteria, enterococci was the only significant organism. Among the 20 isolates of Enterococci, 7 (35%) were resistant to imipenem, 6 (30%) were resistant to ampicillin, 7 (35%) to gentamicin, 9 (45%) to penicillin. None of isolate was resistant to vancomycin.

4.4: Risk factors/Evaluation of empirical therapy

Three criteria were defined to evaluate the empirical therapy of the febrile neutropenic patients. According to those criteria, 92/208 (44.23%) episodes were found to have inappropriate empirical therapy. Bacterial isolates of 39 episodes (42.3%) from all 92 episodes indentified with inappropriate empirical therapy were found to be resistant against the prescribed therapy. Thirty of 92 episodes (32.6%) were found to have delayed in the empirical antibiotic therapy and for remaining 23 of 92 episodes (25.0%) were found to have delayed antifungal therapy (after continuous episode of febrile neutropenia for 7 days). Seven out of theses 23 patients (30.4%) died within 30 days of identification of febrile neutropenia.

Out of 30 episodes with delayed antibacterial therapy, 14, 12 and 4 episodes received empirical antibiotic therapy between 24-48 hours, after 48 hours and after 72 hours of identification of febrile neutropenia, respectively.

Figure-3: Percentages of different causes of inappropriate therapy.



We have tried to find out the answers to several questions, among those most important was to find out the effect of inappropriate antibiotic therapy on the clinical outcome of febrile neutropenic patients. Detailed literature review was conducted to find the other factors which

can affect the clinical outcome of the patients. Patients were divided in to two arms based on antibiotic therapy (appropriate & inappropriate empirical therapy).

Bivariate analysis was conducted first and all the independent variables having significant odd ratio were selected for logistic regression. As for as dependent variable is concerned, it was clinical outcome of the patient and as described in the methodology section two clinical outcomes (LOS & Mortality) were defined. Length of stay was in days as continuous data. Therefore, to conduct binary logistic regression we divided it in to two classes, less than or equal to 45 days and more than 45 days. In bivariate analysis for LOS, inappropriate empirical therapy, vasopresser use, respiratory failure, hematologic malignancy, and neutropenia level <100 cells/ul were significantly associated with clinical outcome of the patients.

Table-11: Independent predictors of length of stay in a bivariate analysis.

Predictor	Odd ratio	95% CI	*P*-value
Inappropriate empirical therapy	6.579	3.390-12.768	0.000
Vasopresser use	2.56	1.363-4.830	0.002
Respiratory failure	2.470	1.340-4.555	0.003
Hematologic malignancy	5.908	3.101-11.253	0.000
Female gender	1.02	0.561-1.860	0.945
Bacteremia	1.53	0.812-2.898	0.186
Neutropenia level<100 cells/ul	2.897	1.11-7.56	0.025
Acute kidney injury	0.769	0.343-1.724	0.523

All these predictors of length of stay were later used in regression model. Hematologic malignancy, inappropriate empirical therapy, vasopresser use, with odd ratios of 5.00, 6.049, 2.23, respectively were significantly associated with the dependent variable. Odd ratios of all the predictors included in regression are given in following table.

Table-12: Independent predictors of length of stay in multivariate logistic regression analysis.

Predictor	Odd ratio	95% CI	*P*-value
Hematologic malignancy	5.00	2.389-10.490	0.000
Respiratory failure	1.041	0.403-2.552	0.976
Vasopresser use	2.232	0.867-5.749	0.036
Inappropriate empirical therapy	6.049	2.877-12.717	0.000
Neutropenia level<100 cells/ul	1.599	0.501-5.100	0.427

All those predictors (covariates) included in the analysis of LOS were also included in the analysis of mortality within 30 days. First of all, bivariate association between each predictor variable and mortality was conducted. Inappropriate empirical therapy, vasopresser use, bacteremia was found to be significantly associated with mortality of the patients as shown in table 13. All these predictors were later used in regression model. Inappropriate empirical therapy and vasopresser use with odd ratios of 4.147 and 8.953 respectively were significantly associated with the dependent variable. Odd ratios of all the predictors included in regression are given below in table 14.

Table-13: Independent predictors of mortality in a bivariate analysis.

Predictor	Odd ratio	95% CI	*P*-value
Inappropriate empirical therapy	4.848	1.722-13.646	0.001
Vasopresser use	11.523	3.745-35.453	0.000
Respiratory failure	1.373	0.564-1.586	0.000
Hematologic malignancy	0.472	0.185-1.201	0.109
Female gender	1.032	0.425-2.509	0.944
Bacteremia	5.824	1.324-25.615	0.009
Acute kidney injury	1.088	0.345-3.425	0.866
Neutropenia level<100 cells/ul	1.146	1.084-1.212	0.059

Table-14: Independent predictors of mortality in multivariate logistic regression analysis.

Predictor	Odd ratio	95% CI	*P*-value
Bacteremia	2.515	0.518-12.202	0.252
Vasopresser use	8.953	2.452-14.450	0.001
Inappropriate empirical therapy	4.147	1.394-12.202	0.011

Bivariate and multivariate logistic regression was also conducted for patients with bacteremia only as shown in table 15-18.

Table-15: Independent predictors of length of stay in a bivariate analysis for patients with bacteremia only

Predictor	Odd ratio	95% CI	*P*-value
Inappropriate empirical therapy	6.000	2.736-13.156	0.000
Vasopresser use	2.725	1.312-5.662	0.007
Respiratory failure	1.688	0.823-3.460	0.152
Hematologic malignancy	5.125	2.386-11.007	0.000
Female gender	1.131	0.554-2.311	0.735
Neutropenia level<100 cells/ul	4.661	0.977-22.25	0.037
Acute kidney injury	0.464	0.176-1.222	0.115

Table-16: Independent predictors of LOS in multivariate logistic regression analysis for patients with bacteremia only

Predictor	Odd ratio	95% CI	*P*-value
Hematologic malignancy	5.234	2.160-12.685	0.000
Vasopresser use	2.192	0.918-5.232	0.077
Inappropriate empirical therapy	6.268	2.589-15.174	0.000
Neutropenia level<100 cells/ul	2.119	0.366-12.254	0.402

Table-17: Independent predictors of mortality in a bivariate analysis for patients with bacteremia only.

Predictor	Odd ratio	95% CI	*P*-value
Inappropriate empirical therapy	6.103	1.308-22.476	0.010
Vasopresser use	7.224	2.291-22.902	0.000
Respiratory failure	0.345	0.269-0.441	0.000
Hematologic malignancy	0.492	0.185-1.305	0.148
Female gender	0.740	0.278-1.967	0.545
Acute kidney injury	0.696	0.189-2.563	0.584
Neutropenia level<100 cells/ul	0.891	0.836-0.949	0.217

Table-18: Independent predictors of mortality in multivariate logistic regression analysis for patients with bacteremia only.

Predictor	Odd ratio	95% CI	*P*-value
Vasopresser use	6.528	1.089-25.174	0.038
Inappropriate empirical therapy	5.343	1.382-18.660	0.015

Successful outcome of the patients after empirical antibiotic therapy was defined as the cure of infection within 5 days judged by all symptoms of infection including body temperature, heart rate and respiratory rate. It was difficult to find covariates or other predictors for good outcome as a dependent variable. Bivariate analysis and T-test to compare the means of LOS both groups were conducted. In bivariate analysis appropriate empirical antibiotic therapy with the odd ratio 10.756 (95%CI 5.337-21.513) was significantly associated with the good clinical

outcome of the patients. Mean of days till cure from both groups, appropriate empirical therapy and inappropriate empirical therapy was 5.16 and 10.28 respectively, with mean difference of 5.125 and (P=0.003), were significantly different from each other.

Chapter 5

Discussion/Conclusion

Bacterial etiology is often unidentified at the onset of infection. Awareness of the prevalence of causative bacteria in neutropenic patients with fever is important since timely adequate antimicrobial therapy is of vital importance. The spectrum of bacterial isolates from all specimens in our study is similar to what has been reported in other studies. Two hundred (73.5%) organisms were gram negative and 59 (21.6%) were gram-positive bacteria. Among gram negative bacteria, *E.coli* with the percentage of 21.6% remained predominant organisms. But for microorganism isolated from patients with bacteremia, the spectrum of bacterial pathogen in our study was totally different from other studies. In most of other previous studies gram positive pathogens were the predominant organisms causing bacteremia. The etiology of febrile neutropenia, as reported in the literature, is subject to variations that are dependent on a variety of factors. Use of prophylaxis can have profound effect on the type of bacterial pathogens seen in febrile neutropenic patients. It depends upon the policy of hospital in local setting, like in Songklanagarind hospital where this was conducted no prophylaxis for gram negative bacteria was administered which could be the one reason to have gram negative bacteria in access. The increased use of indwelling catheters, allowing colonization and infection by skin flora, mostly gram-positive organisms, is also a major factor. The nature of the chemotherapy used has also been reported to influence the bacterial etiology of febrile neutropenia. The use of more specific agents with less cytotoxic potential and, therefore, less mucosal toxicity can lead to a reduction in infections due to viridans streptococci, enterococci, and enteric gram-negative organisms.

E.coli and *K. pneumoniae* with the aggregate percentage of 41.1% (112) were the two most frequently isolated microorganisms. Local antibiogram of Songklanagarind hospital in 2010 shows (73.0%) of *K. pneumoniae* was susceptible to piperacillin/tazobactam, 99% of them were susceptible to imipenem and (94%) of *E.coli* was susceptible to piperacillin/tazobactam, while (100%) susceptible to imipenem. Which is quite similar to the susceptibility of *E.coli* and *K.pneumoniae* towards imipenem and piperacillin/tazobactam,

given in our study. Seventy five percentage of *K. pneumoniae* was susceptible to piperacillin/tazobactam, 98% of them were susceptible of imipenem and 96% of *E.coli* were susceptible to piperacillin/tazobactam, while 99% susceptible to imipenem. *Enterococci* was the only significant organism from Gram-positive bacteria. Among the 20 isolates of Enterococci, (65%) were susceptible to imipenem, (70%) were susceptible to ampicillin, (65%) to gentamicin, (55%) to penicillin. While susceptibility to vancomycin was (100%). Local antibiogram showed that, (76%) were susceptible to imipenem, (74%) were susceptible to ampicillin, (60%) to gentamicin, (59%) to penicillin and (100%) to vancomycin. We have found that among the 38 isolates of *P. aeruginosa*, (77%) were susceptible to imipenem and (92%) were susceptible to piperacillin/tazobactam. While local antibiogram showed 81%, 82% susceptible to imipenem and piperacillin/tazobactam respectively. For some bacteria/antimicrobial Susceptibility results are significantly different as given in antibiogram of the Songklanagarind hospital, but the difference in sample size is so large, that it would be difficult to compare present study with antibiogram and conclude that resistance patterns of bacteria found in febrile neutropenic patients are different from local resistance patterns, like only 38 isolates of *P. aeruginosa* were available while in local antibiogram 1,489 isolates were included.

Many studies have reported various response rates to empirical therapy from 50-70%.[8] One of the reasons for low response to empirical therapy can be inappropriate empirical therapy. It was found in our study that 92 (44.23%) patients were prescribed with inappropriate empirical therapy. Bacterial isolates of 40 patients out of 92 (43.4%) were found to be resistant against the prescribed therapy. Different organisms were found to be resistant to the prescribed therapy. There was no single organism with significant numbers to be recognized as cause of the problem solely. Most of them were gram negative organisms including *E.coli, P. aeruginosa* and *K. pneumoniae*. At our institute, piperacillin/tazobactam is considered as a favorable choice and it is one of the most commonly prescribed antibiotics to the febrile neutropenic patients, but high resistance (24.5%) to piperacillin/tazobactam in *Klebsiella pneumonia* was found, which is the second most commonly found organism. It is suggested to consider number of episodes of febrile neutropenia and length of stay as risk factors for resistant organisms, as we have found that resistance to piperacillin/tazobactam

increased with increasing length of stay and with consecutive episodes of febrile neutropenia. It could be because of prior exposure to antimicrobial therapy or because of being in contact with resistant organisms from hospital. According to IDSA empirical antifungal coverage should be considered in patients who have persistent fever after 4–7 days of a broad-spectrum antibacterial regimen. Twenty three patients out of 92 (25.0%) in our study were not prescribed with fungal therapy after continuous episode of febrile neutropenia for 7 days. Seven out of theses 23 patients (30.4%) died within 30 days of identification of febrile neutropenia, considering high mortality rate in patients without fungal therapy. In addition to changes in combination broad-spectrum antibiotics, starting antifungal therapy would be the appropriate response. Although preemptive antifungal therapy is accepted as alternative to empirical fungal therapy but the quality and strength of evidence is weak as compared to the recommendation of starting empirical antifungal therapy after 7 days of continuous febrile neutropenia. One randomized control trial indicates that preemptive treatment increased the incidence of invasive fungal disease, without increasing mortality. Empirical treatment may provide better survival rates for patients receiving induction chemotherapy.[55] One study stated high percentage, 15-45% of patients with a continuous neutropenic fever were estimated to have IFI.[56] There are some other reasons also, supporting to use antifungal therapy before a definitive diagnosis of infection e.g. 1) IFI is difficult to diagnose during the neutropenic period, 2) the delay of antifungal therapy to definitive diagnosis can easily provoke disseminated infection, and 3) IFI (*Candida* or *Aspergillus* species in most cases) that had not been clinically documented was found, in the autopsy of patients who died of neutropenic fever and a continuous fever was the only initial sign of IFI .[56-59] Thirty episodes out of 92 (32.6%) were found to have delay in the empirical antibiotic therapy. Besides the resistant organisms and absence of antifungal therapy, delay in the empirical therapy can affect the clinical outcome of the patients. Specifically in case of neutropenia as we know that neutrophils are the predominant leukocytes in the blood and are the first line of defense in controlling bacteria invading the blood stream.[60] In one such study the impact of delay of active antimicrobial therapy on mortality was found to vary by level of neutropenia. In adjusted analysis, delay was not significantly associated with increased mortality among patients who either were nonneutropenic or had ANCs of 100 to 500 cells/μL. However, for non-ICU patients with ANCs of <100 cells/μL, delay was associated with statistically significant 18-fold-increased odds of death, while for ICU patients

with ANCs of <100 cells/μL, delay was associated with nearly significant 5-fold increased odds of death.[43]

Although large proportion of the patients was found to be prescribed with inappropriate empirical therapy, but the effect of inappropriate empirical therapy on the clinical outcome of the patient was still need to be found, so taking length of stay and mortality as a parameter for clinical outcome, data from the patients of this study was planned to compared. Many studies conducted in different parts of world tried to evaluate the effectiveness of different antibiotics by comparing several antibiotics with each other or comparing between monotherapy and combination therapy, but none tried to find out the effect of inappropriate therapy on clinical outcome of febrile neutropenia patients, or to find out that up to what extent clinical outcome of patients receiving inappropriate empirical would differ from the patients receiving appropriate empirical therapy, irrespective of what antibiotics been used. Several studies have been conducted in non febrile neutropenic patients and almost all of them were either focused on specific antimicrobial agent or specific organism but not on the specific condition like we did for febrile neutropenic patients. Although it is reasonable to expect inadequate antimicrobial therapy to worsen mortality, this relationship is complex and not consistently supported in the literature. While several studies have shown an association between inappropriate antimicrobial therapy and mortality[61-63], other studies have not found a significant association.[64-66]

Detailed literature review was conducted to find the others factors which can affect the clinical outcome of the patients and can be used as covariates with inappropriate empirical therapy. In multivariate analysis inappropriate empirical therapy and vasopresser use were significantly associated with the increase in mortality and Hematologic malignancy, inappropriate empirical therapy, vasopresser use were significantly associated with the increase in length of stay. In most of the other studies lungs was identified as one of the predominant site of infection and pneumonia as one of the important factor for increase in length of stay and mortality, but unlike other studies lungs were not the predominant site of infection, in fact the number was too low to used it as a covariates with inappropriate empirical therapy.

In this study, LOS and mortality was evaluated as an outcome of interest as a substantial proportion of the health care costs incurred by patients with cancer can be attributed

directly or indirectly to the treatment of FN. Longer periods of hospitalization increase cost and negatively affect the quality of life of affected patients. Beside the type of cancer and vasopresser use, our study shows that inappropriate empirical antimicrobial therapy was significantly associated with longer LOS and mortality. To the best of our knowledge, this association has not been reported previously among patients with FN.

Recent randomized controlled clinical trials of empiric antimicrobial therapy of febrile neutropenia are notable in that significantly different response rates between treatment regimens are rarely demonstrated. Based on this observation and on previous research, one might conclude that these regimens are interchangeable. However, striking differences among regimens emerge when the time to clinical response is examined. In this respect, one regimen was superior to other regimen. Although results from present study provide support for the notion that otherwise antibiotic regimens with similar response may differ in clinical response time, this was not a formal trial of specific antibiotic regimens. However, a recent randomized trial contains similar findings. Freifeld et al report that at 72 hours of therapy, 74% of patients receiving imipenem had defervesced compared with only 60% of those receiving ceftazidime ($P = .02$).[67]

The limitations of this study are inherent to studies based on administrative data. This study was retrospective in design. Detailed clinical information specifically subjective clinical information was limited. The small sample size and single center study has several limitations. This data set includes all patients admitted to the hospital not selected by any criteria other than febrile neutropenia, cancer and positive cultures. Although we defined criteria to select culture results from non sterile sites, but still there is a possibility that some of them could be contaminated. There are some others covariates like length of ICU stay, APACHE score and MASCC risk index, which were not included in the study. Additional information regarding socioeconomic status and delay in treatment could be possible if sample size, duration of study and number of centers is increased. We set criteria to evaluate dose in certain clinical conditions but other than dose of antimicrobials were not evaluated.

Despite the widespread approach of treating all FN neutropenic patients with empiric broad spectrum antibiotics for potential bacteremia, FN with cancer remains associated with a

significant, increase in length of stay and mortality. This suggests that effectiveness of empirical therapy and certain host or disease-related factors may play a role in influencing mortality resulting from FN.

Conclusion

In summary, this study found that trend of bacterial isolates was consistent with other studies. patients with neutropenia, were at increased risk of death and longer length of stay when exposed to inappropriate empirical therapy, Hematologic malignancy and vasopresser use, it was also found that patients exposed to inappropriate empirical therapy had longer time to respond to the therapy which is then an important factor regarding the cost of treatment. Clinicians should consider starting empirical antifungal therapy after continuous fever for 5-7 days and taking in to consideration the high resistance level to piperacillin/tazobactam it is suggested to consider number of episodes of febrile neutropenia and length of stay as we have found that resistance to piperacillin/tazobactam increased with increasing length of stay and with consecutive episodes of febrile neutropenia.

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Appendix

Data Collection Form

Patient identification:

Pt. no..... Age ..... Sex ..... Weight .....

Type of cancer: Solid tumor ☐ Hematologic malignancy ☐

Infection data:

Date of diagnose	Infection site	Organisms	Antimicrobial therapy				
			Date & time		Antibiotic & Dose	Type of Tx*	NO of doses
			Started	Stopped			

*Type of Tx: E=Empirical therapy, D=Documented therapy

Administered with in 24 hours of diagnoses of febrile neutropenia. ☐

Administered after 24 hours. ☐

Clinical Data:

Cultured organism: ..... Site of specimen .....

Date		Specimen	Organism	Susceptibility
Collected	Reported			

Laboratory data and vital signs:

	Date & Time	Dates												
Date														
ANC														
B.Temp*														
Culture														
Heart rate														
Resp.rate														
Creatinine level														

Vasopressers use: Yes ☐ No ☐ Respiratory failure : Yes ☐ No ☐

Acute renal failure: Yes ☐ No ☐ Bacteremia: Yes ☐ No ☐

Length of stay: .....Neutropenia level :.....

Date/time infection cured: ..... Mortality Date/time: .....

Type of organisms : .....

Site specific Sign & symptoms of infection .....

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List of Publication and Proceedings

Febrile neutropenia in cancer patients; microbiology and empirical antibiotic therapy. ASEAN Academic society international conference 2012