A STUDY ON EFFECTIVENESS AND SAFETY USE OF ANTIBIOTICS IN FEBRILE NEUTROPENIC PATIENTS WITH SOLID TUMOR AND HEMATOLOGICAL MALIGNANCIES
IN
KING FAHAD SPECIALIST HOSPITAL
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By

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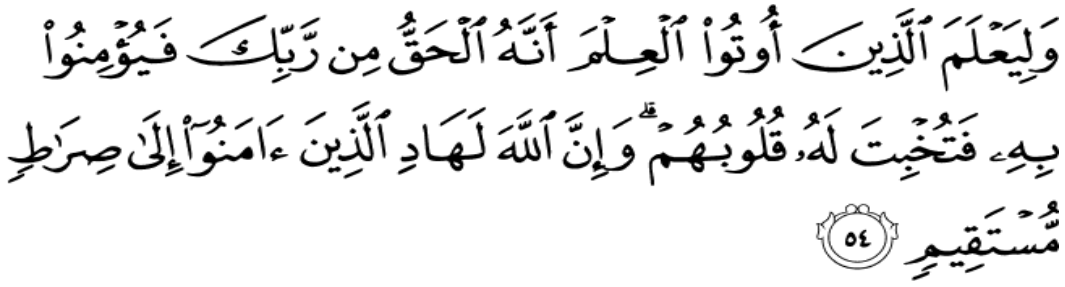
DEDICATION

In the name of Allah, the beneficent, the merciful. And praise belongs to Allah, Lord of the universe.

I am dedicating this thesis to my beloved family and parents.

I dedicate this research work to the gentlemen and leaders who have a special place in my heart and who taught me perseverance and access to the best and work sincerely, and who still followed them in my life.

Allah says in the holy Quran



"And that those who have been given knowledge may know that it (this Qur'aan) is the truth from your Lord, so that they may believe therein, and their hearts may submit to it with humility" [al-Hajj 22:54] .

I believed on the statement of our Prophet Muhammad (Peace be upon him) says, **"No two things have been combined better than Knowledge and Patience"**

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LIST OF ABBREVIATIONS

ABVD	Rituximab+cyclophosphamide+etoposide+vincristine
AG	Aminoglycosides
ALT	Alanine transaminase
ALP	Alkaline phosphatase
AM	Amikacin
ANC	Absolute neutropbil count
ANOVA	Analysis of variance
AST	Aspartate transaminase
ASCO	American society of clinical oncology
BP	Blood Pressure
BUN	Blood urea nitrogen
Ca	Cancer
CDI	Clinically defined infections
CF	Ciprofloxacin
CIN	Chemotherapy induced neutropenia
CI	Confidance interval
CHOP	Cyclophosphamide+doxorubicin+vincristine
CoNS	Coagulase negative staphylococcus
Cr	Creatinine
Cr Cl	Creatinine clearance
CSLI	Clinical and laboratory standard institute

CT	Computerized tomography
CT	Ceftrioxone
CZ	Cefazoline
Ep	Episodes
ESMO	European society for medical oncology
ESBL	Extended spectrum beta lactamase
EORTC-IATCG	European organization for research treatment of cancer-International antimicrobial therapy cooperative group
F	Female
F˚	Fahrenheit
FUO	Fever of unknown origin
G-CSF	Granulocyte-colony stimulating factor
GCC	Gulf co-operation council countries
g/dl	Gram per deciliter
GGT	Gama Glutamyl tranferase
GM	Gentamycin
GLOBACON	Global observatory cancer
Hg	Hemoglobin
HICPAC	Hospital infection control practice advisory committee
HIP	High dose imipenem
HIPA	High dose imipenem plus amikacin
HIPV	High dose imipenem plus vancomycin
IARC	International agency for research on cancer

IC	Imipenem-cilastatin
IRB	Institutional Review Board
IDSA	Infectious disease society of America
IHO	Infectious diseases working party of the German society of hematology and oncology
ITT	Intention to treat
LF	Levofloxacin
LIPV	Low dose imipenem plus vancomycin
LZ	Linezolid
M	Male
MDI	Microbiologically defined infections
Mg	Magnesium
mmol/L	Millimole per liter
MPV	Mean platelet volume
MRSA	Methicillin resistant staphylococcus aureus
NC	Not computed
NCCN	National comprehensive cancer network
NHL	Non-hodgkin’s lymphoma
NHANES	National health and nutrition examination survey
OR	Odds ratio
Pt	Patient
PT	Piperacillin-tazobactam
R-CVP	Rituximab+cyclophosphamide+vincristine

R-CHOP	Rituximab+cyclophosphamide+doxorubicin+vincristine
SENTRY	Antimicrobial survivelance program
SEQ	Chemotherapy society of Spain
Spp	Species
U/L	Unit per liter
VM	Vancomycin
VRE	Vancomycin resistant enterococci
WBC	White blood cells

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KAJIAN KEBERKESANAN DAN KESELAMATAN DALAM PENGGUNAAN ANTIBIOTIK-ANTIBIOTIK BAGI PESAKIT-PESAKIT NEUTROPENIA FEBRIL YANG MENGALAMI TUMOR PEPEJAL DAN HEMATOLOGI DI HOSPITAL PAKAR RAJA FAHAD, SAUDI ARABIA

ABSTRAK

Neutropenia adalah faktor pendorong bagi pesakit-pesakit kanser mengalami komplikasi dan jangkitan-jangkitan teruk terutamanya patogen-patogen gram negatif dan positif. Pengetahuan tentang isolat-isolat bakteria yang menyebabkan neutropenia febril adalah sangat penting bagi memulakan terapi antibiotik empirik yang dianggap sebagai suatu kecemasan perubatan di dalam pesakit-pesakit berisiko tinggi.Justeru itu, objektif utama kajian ini adalah untuk menilai keberkesanan dan keselamatan berkaitan dengan terapi antibiotik yang diberikan secara tunggal dan gabungan dalam pesakit neutropenia febril yang mengalami kanser pepejal dan hematologi.Suatu kajian eksploratori dan deskriptif telah dilakukan secara retrospektif dalam kalangan pesakit-pesakit dewasa (umur > 16 tahun) neutropenia febril yang mengalami kanser pepejal dan hematologi, dimasukkan antara Mei 2008 dan Mei 2013 di Hospital Pakar Raja Fahad, Damman, Saudi Arabia. Daripada sejumlah 1748, hanya 258 pesakit-pesakit saja layak terlibat dalam kajian ini. Malignansi-malignansi terbanyak merangkumi 51.16% (132/258) hematologi dan 48.84% (126/258). pepejal. Sejumlah 138 isolat-isolat bakteria dikenalpasti dalam 106 jankitan-jangkitan yang terbukti secara mikrobiologi di dalam pesakit-pesakit neutropenia febril. Telah didapati bahawa prevalens patogen-patogen gram negatif adalah 65.94% (91/138), manakala 34.06% (47/138) adalah

gram-positif.. Telah diperhatikan bahawa terdapat kadar tinggi bagi ESBL-ESBL kalangan *Escherichia coli* (38%) dan *Klebsiella pneumoniae* (22.22%) serta meningkatnya rintangan imipenem-cilastatin kalangan *Pseudomonas aeruginosa* (18.84%);manakala kadar MRSA adalah 28.72%. Daripada sejumlah 258, 96 pesakit-pesakit telah di rawat secara terapi tunggal dengan piperacillin-tazobactam(PT), vancomycin (VM) dan aminoglikosida (AG) telah ditambah pada terapi awal PT dan IC dalam 117 pesakit-pesakit. Terapi dalam kalangan 45 pesakit-pesakit telah diubahsuai. Kadar respons terapi tunggal PT adalah lebih tinggi dalam kalangan pesakit-pesakit berumur antara 51-92 tahun (P=0.041) serta mereka yang mengalami neutropenia aruhan kemoterapi (P=0.026) setelah 12 hari menerima administrasi kemoterapi berbanding dengan kadar respons pada terapi-terapi PT+AG dan PT+VM. Dalam malignansi-malignansi tumor pepejal, keabnormalan klinikal yang signifikan, seperti alkalina fosfatas, adalah tinggi dalam kalangan pesakit-pesakit yang dirawat secara terapi tunggal PT (P=0.016) berbanding dengan terapi PT+VM. Peningkatan dalam tekanan darah (P=0.005), pengurangan paras hemoglobin (P=0.006) dan pengurangan dalam pengiraan sel-sel darah putih (P=0.032) telah diperhatikan dalam pesakit-pesakit yang dirawat dengan terapi gabungan (PT + VM dan PT + AG).Kesimpulannya, penemuan penyelidikan ini telah mengambarkan bahawa prevalens organisme-organisme gram-negatif serta tapak-tapak isolasinya adalah sejajar dengan kajian-kajian antarabangsa. Sebaliknya, terdapat perbezaan dalam corak spektrum bakteria dan suseptibiliti. Seterusnya, kajian ini telah memperlihatkan bahawa tekanan darah meningkat dan paras hemoglobin serta pengiraan sel-sel darah putih telah berkurangan apabila VM atau AG ditambahkan pada terapi awal PT. Berlandaskan pada epidemiologi dan antibiogram-antibiogram tempatan, kami mencadangkan tambahan VM dan AG pada

terapi piawai apabila berdepan dengan jangkitan-jangkitan bakteria Gram-positif dan Gram-negatif yang rintang.

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ABSTRACT

Neutropenia is a predisposing factor of serious complications and potentially life-threatening infections in patients with malignancies, particularly Gram-negative and Gram-positive infections. The local spectrum and sensitivity of bacterial isolates causing febrile neutropenia should be identified because facilitating appropriate empirical antibiotic therapies is considered as a medical emergency for these high-risk patients. Therefore, this study mainly aimed to evaluate the effectiveness and safety associated with single and combined antibiotic therapies for febrile neutropenic patients with solid tumor and hematological malignancies.An exploratory and descriptive study was conducted retrospectively among adult (age > 16 years) febrile neutropenic patients with solid tumor and hematological malignancies admitted between May 2008 and May 2013 at the King Fahad Specialist Hospital, Dammam, Saudi Arabia. Of 1,748 patients, 258 were eligible to be included in the study. The majority of malignancies affecting 51.16% (132/258) of the patients was hematological. The remaining 48.84% (126/258) of the patients manifested solid tumor malignancies. A total of 138 bacterial isolates were identified in 106 microbiologically documented infections in the febrile neutropenic patients. The overall prevalence of Gram-negative infections was 65.94% (91/138). By contrast, the overall prevalence of Gram-positive infections was 34.06% (47/138). The rates of extended-spectrum beta-lactamase production among *Escherichia coli*

(38%) and *Klebsiella pneumonia* (22.22%) were high. The resistance to imipenem–cilastatin (IC) treatment of *Pseudomonas aeruginosa* (18.84%) increased. The rate of occurrence of methicillin-resistant *Staphylococcus aureus* was 28.72%. Of the 258 patients, 96 were treated with piperacillin–tazobactam (PT) monotherapy. Vancomycin (VM) and aminoglycosides (AG) were added to the initial PT and IC therapy for 117 patients. The therapy for 45 patients was modified. The response rates to PT therapy of the patients aged between 51 and 92 years (P=0.041) and those who developed chemotherapy-induced neutropenia (P=0.026) after 12 days of chemotherapy administration were higher than their corresponding response rates to PT + AG and PT + VM therapies. In solid tumor malignancies, clinically significant abnormalities, such as alkaline phosphatase, were higher in the patients treated with PT monotherapy (P=0.016) than in the patients subjected to PT + VM therapy. Increased blood pressure (P=0.005), decreased hemoglobin levels (P=0.006) and decreased white blood cell counts (P=0.032) were observed in the patients treated with dual therapies (PT + VM and PT + AG). In conclusion, the prevalence of Gram-negative bacteria and the isolation sites of these microorganisms were similar to those described in other international studies. Conversely, different trends were observed in terms of bacterial spectrum and susceptibility patterns. Our results confirmed that PT is effective and safe for monotherapy. Our study further revealed that blood pressure increased and hemoglobin levels and white blood cell counts decreased when VM or AG was added to the initial PT therapy. On the basis of local epidemiology and antibiograms, we recommend the addition of VM and AG to standard therapy when resistant Gram-positive and Gram-negative bacterial infections are encountered.

CHAPTER 1

INTRODUCTION

1.1 Historical background of neutropenia

Neutropenia is a hematological disorder characterized by an abnormal decrease in the absolute number of neutrophils or an expected decrease to <500 cells/mm^3 in the next 48 h (Bow, 2005; Freifeld *et al.*, 2011; National Comprehensive Cancer, 2013). Neutrophils are white blood cells (WBCs) produced in the bone marrow and they account for approximately 60% of blood. These cells serve as primary defense against infections by destroying pathogens in blood (Frey, 1999; Simmons). These WBCs are also the first cellular components that function in inflammatory and infectious responses (Crawford, Dale, & Lyman, 2004). In patients with malignancies, neutropenia is a predisposing factor of serious complications and potentially life-threatening infections caused by Gram-negative and Gram-positive pathogens. In chronic neutropenia, a rapid decrease in neutrophil count indicates a high risk of acquiring a life-threatening infection (Glauser, 2000; Link *et al.*, 2003). If neutropenia lasts less than 7–10 days, the risk of infection is low. By contrast, the risk of infection is high if the condition exceeds 10 days. Therefore, the risk of infection and mortality correlate with the degree of severity, the duration of neutropenia and the presence of fever (Gerald P. Bodey, Rodriguez, Chang, & Narboni, 1978; Caggiano, Weiss, Rickert, & Linde-Zwirble, 2005).

Neutropenia is categorized as mild, moderate or severe (Baehner, 2003). This condition is also classified by the Severe Chronic Neutropenia International Registry into two forms: congenital, which occurs by birth, and acquired, which manifests at

any time throughout life. Congenital or Kostmann neutropenia is further defined as maturation arrest in the early stages of neutrophil development in the bone marrow. Autoimmune neutropenia is a condition involving the destruction of the body's own blood neutrophils by neutrophil-specific antibodies (David C Dale *et al.*, 2003). The concentration of neutrophils in blood is influenced by age, genetics and environmental factors. In certain geographical areas, some populations yield different neutrophil blood concentrations. For instance, populations of African descent possess lower normal neutrophil blood concentrations than those of European descent (Lichtman, 2006).

1.2 Causes of neutropenia

Several risk factors influence the onset of neutropenia. The common risk factors of neutropenia are hematological disorders, autoimmune disease, drug reactions, chemotherapy and radiation therapy. The general risk factors of the development of severe neutropenia are old age and performance status because mature neutrophil production is lower in old population than in young individuals. Furthermore, the incidence of neutropenia is higher in females than in males (Crawford *et al.*, 2004; B. A. Rasool Hassan, Yusoff, & Othman, 2010; Lyman, Lyman, & Agboola, 2005). The presence of comorbid conditions, such as liver, renal and cardiovascular diseases, also increases the risk of developing neutropenia. Likewise, sepsis, pneumonia, hypertension and chronic pulmonary disease exacerbate neutropenic complications. Other indicators of neutropenia include decreased white blood cell counts and low hemoglobin and serum albumin concentrations (Crawford *et al.*, 2004; B. A. Rasool Hassan *et al.*, 2010; Lyman *et al.*, 2005).

Neutropenia is often diagnosed in patients with hematological malignancies. Under this condition, neutrophil production decreases as bone marrow and hematopoietic stem cells are destroyed and thus possibly results in neutropenia. These patients may also be at risk of infectious complications and require thorough examination (Boxer, 2012; B. A. Rasool Hassan *et al.*, 2010).

Cytotoxic chemotherapy regimens and radiation therapy predictably suppress the hematopoietic system and destroy the bone marrow; these conditions decrease neutrophil counts and thus increase the susceptibility to infection of patients (Crawford *et al.*, 2004; B. A. Rasool Hassan *et al.*, 2010; Lyman *et al.*, 2005; Takenaka *et al.*, 2013). High doses of cyclophosphamide, etoposide and anthracyclines are significant predictors of severe neutropenia (Lyman *et al.*, 2005).

Other drugs, such as clozapine, antithyroid drugs, sulfasalazine, ticlopidine, angiotensin converting enzyme inhibitors, H2 blockers, nonsteroidal anti-inflammatory drugs and antiarrhythmic drugs (e.g., tocainide, procainamide and dapsone), are also predictors of severe neutropenia. Drugs, such as colchicine, azathioprine, ganciclovir and methotrexate, suppress bone marrow functions (Baehner, 2003). Chlorpromazine and allopurinol, which are diuretics, also cause neutropenia (B. A. Rasool Hassan *et al.*, 2010).

1.3 Pathophysiology of neutropenia

Neutrophils are the most abundant type of WBCs; they constitute an essential part of the innate immune system and first line of defense. Neutrophils are also known as granulocytes or polymorphonuclear segmented cells and they account for 60%–70% of circulating absolute neutrophil count (Bhatt & Saleem, 2004). In host defense,

neutrophils rapidly respond to invading microorganisms (Witko-Sarsat, Rieu, Descamps-Latscha, Lesavre, & Halbwachs-Mecarelli, 2000).

In the bone marrow, mature neutrophils are produced by precursors in 10–14 days. These cells then enter the blood pool without re-entry into the marrow. The life span of neutrophils is very short (i.e., only 4–8 h); thus, the bone marrow must continuously produce neutrophils. These neutrophils leave the blood pool and subsequently enter tissues or infected sites, where they perform cellular action or die. Chemotherapy triggers bone marrow suppression and stem cell destruction, which decrease neutrophil production. Mature cells die and remain unreplaced; as a consequence, the body's ability to fight infection weakens (D. C. Dale, 2005; Goodwin & Braden; O'Leary, 2010).

1.4 Etiology of fever, infection and microbial spectrum

1.4.1 Etiology of fever in neutropenia

Fever may be the most common manifestation of infection in a neutropenic patient. Cancer patients with febrile neutropenia present with fever manifested by single oral temperature measurement of >38.3 °C (101 ° F) or a temperature of >38.0 °C (100.4 °F) sustained for 1 h (Bošnjak, 2004; Bow, 2005; De Naurois, Novitzky-Basso, Gill, Marti, Cullen, & Roila, 2010; Freifeld *et al.*, 2011; National Comprehensive Cancer, 2013).

Fever often occurs in 48% of episodes when the neutrophil count decreases below 100 cells/mm^3 and 70% of febrile episodes manifest when the neutrophil count is <500 cells/mm^3. Only 10% of febrile episodes are observed in patients whose neutrophil count is >2000 cells/mm^3. Depending on infection, the proportion of fever varies from 49% to 68% (Gerald P. Bodey *et al.*, 1978).

Approximately 10%–50% of patients with solid tumor suffer from fever, whereas 80% of neutropenic patients with hematological malignancies develop fever after 7–12 days of chemotherapy regimen (Klastersky, 2004; Legrand, Max, Schlemmer, Azoulay, & Gachot, 2011). The 20%–55% of neutropenic patients manifest fever because of bacterial infections after they undergo chemotherapy (Ammann, Hirt, Lüthy, & Aebi, 2003).

In addition to bacterial and fungal infectious agents, noninfectious agents, such as blood transfusion, some drugs (azathioprine, allopurinal, gancyclovir, methotrexate and procainamide) and granulocyte colony-stimulating factors (GCS-F), trigger fever in neutropenic patients. Although bacterial infection rapidly develops in neutropenic cancer patients, signs of inflammatory response are rarely observed. Thus, history of associated diseases, currently used drugs, latest chemotherapy and family background of patients should be thoroughly evaluated. Physical examination involving infection site inspection and bone marrow biopsy should also be conducted; infection sites for inspection include the oral mucosa, sinuses, chest, ear, skin, nails, anal area, vaginal area and catheter insertion sites (Lee *et al.*, 2011).

1.4.2 Epidemiology of infection in neutropenia

The incidence of infection is 14% in patients with neutrophil counts below 500–1000 cells/mm^3. WBC count rapidly decreases as the duration of neutropenia prolongs (Kanneth V. I. Rolston, 2009).

1.4.2 (a) Classification of Infections

Febrile episodes are classified into three groups.

1.4.2.1(a)i Microbiologically Defined Infections (MDI): These episodes involve fever and microbial isolation (Kanneth V. I. Rolston, 2009).

1.4.2.1(b)ii Clinically Defined Infections (CDI): These episodes involve a defined site of infection (pneumonia, enterocolitis or cellulite) but lack microbiological confirmation (Kanneth V. I. Rolston, 2009).

1.4.2.1(c)iii Fever of Unknown Origin (FUO): These episodes are characterized by fever without clinical causes or microbiological documentation of infection. These episodes are also referred to as "episodes of unexplained fever" (Kanneth V. I. Rolston, 2009).

1.4.2(b) Bacterial infection

Bacterial infections generally occur in the initial phases of febrile neutropenia; by contrast, fungal infections frequently occur in prolonged and severe neutropenia (Gabay & Tanzy, 2010; Kenneth V. I. Rolston & Bodey, 2011). More than 60% of neutropenic patients who become febrile are at risk of infection (Billote, Mendoza, & Baylon, 1997; Gençer, Salepçi, & Özer, 2003). Bacteremia accounts for 35% of hematological malignancies and 20% of solid tumor malignancies. A high mortality rate is also associated with polymicrobial infections (Viscoli, Varnier, & Machetti, 2005).

1.4.2(c) Fungal infections

Approximately 20% of patients with neutropenia suffer from invasive fungal infections (Eltahawy, 2003). Fungal infections usually occur after a long duration of broad-spectrum antibiotic therapy. Common fungal infections and serious complications in neutropenic patients are caused by *Aspergillus* species and *Candida* species, such as *C. albicans*, *C. tropicalis* and *C. glabrata* (Eltahawy, 2003). Fungal infections may become a primary concern for patients with prolonged neutropenia (B. A. Rasool Hassan *et al.*, 2010).

1.4.2(d) Viral infections

Viral infections are common in patients with impaired cellular immunity but not in patients with neutropenia (Kenneth V. I. Rolston & Bodey, 2011). Viral infections mostly occur in bone marrow recipients. The most common viruses are herpes simplex, cytomegalovirus and varicella zoster (B. A. Rasool Hassan *et al.*, 2010).

1.4.2(e) Site of infection

The common infection sites in febrile neutropenic malignant patients are bloodstream, respiratory tract, urinary tract, skin/skin structures and gastrointestinal tract (Viscoli *et al*, 2005; Rolston, 2009; Nesher *et al*., 2014). A study conducted by the University of Texas M. D. Anderson Cancer Center has revealed that tissue-based infections, such as pneumonia, urinary tract infections and soft tissue infections caused by Gram-negative organisms, are more common than bloodstream-based infections (Sipsas, Bodey, & Kontoyiannis, 2005).

1.4.3 Bacterial spectrum in neutropenia

Bacterial infection is a primary cause of fever in 25% of neutropenic cancer patients; conversely, fungal infections cause fever in 5% of neutropenic patients (Collin, Leather, Wingard, & Ramphal, 2001). Infections in febrile neutropenia are caused by Gram-positive or Gram-negative organisms, fungi or even viruses (Bal & Gould, 2007; B. A. Rasool Hassan *et al.*, 2010).

Gram-negative organisms were predominant in the 1960s until the 1980s. Approximately 60%–80% of these infections were microbiologically documented. The most predominant organisms are Gram-negative bacteria; most of these bacteria are β-lactamase producers, such as *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella* spp. *P. aeruginosa* and *Staphylococcus aureus* infections yield high

mortality rates (Eltahawy, 2003; Kanamaru & Tatsumi, 2004; Okereke & Dudley, 1998; Zinner, 1999).

In the late 1980s, the multicenter trials conducted by the European Organization for Research and Treatment of Cancer–International Antimicrobial Therapy Cooperative Group (EORTC–IATCG) showed that the rate of Gram-positive infections steadily increased to 60%–70%. Coagulase-negative staphylococci and *S. aureus* are predominant bacterial agents of infections. Overall, the EORTC studies from 1973 to 1993 demonstrated a shift from Gram-negative organisms to Gram-positive organisms in microbiologically documented infections in febrile neutropenic cancer patients (Eltahawy, 2003; Glasmacher *et al.*, 2005; Kanamaru & Tatsumi, 2004; Swati, Gita, Sujata, Farah, & Preeti, 2010; Zinner, 1999). The same trials revealed that the rate of Gram-negative infections decreased from 71% to 31% (Swati *et al.*, 2010).

An EORTC review reported that the incidence rates of Gram-negative and Gram-positive infections between 1993 and 2000 were similar (12% and 13%, respectively), with a significant increase in the rate of Gram-negative infections (Glasmacher *et al.*, 2005).

However, the reason for this change in the spectrum of pathogens remains unclear (Viscoli, 1998). Studies have assumed that the shift from Gram-negative infections to Gram-positive infections is due to long-term indwelling catheters, aggressive chemotherapy, continuous evolution of antibiotic use and changes in clinical and local antibiotic resistance (Ramphal, 2004; Viscoli *et al.*, 2005).

The spectrum of infectious pathogens has further changed. Studies in the US and Europe have reported the re-emergence of Gram-negative bacteria in neutropenic

cancer patients (Gençer *et al.*, 2003; Ramphal, 2004; Swati *et al.*, 2010; M. Walwyn, A. Nicholson, M. G. Lee, G. Wharfe, & M. A. Frankson, 2010). Gençer *et al.* (2003) isolated 74.4% of Gram-negative organisms from neutropenic cancer patients and found that *E. coli* (31%) is the most predominant, followed by *K. pneumoniae* (18%), *P. aeruginosa* (13%) and *Streptococcus pneumoniae* (13%).

El Saghir et al. (1989) revealed that Gram-negative and Gram-positive isolates respectively account for 51% and 26% of infections in acute leukemia in Riyadh, Saudi Arabia. Kanafani et al. (2007) performed a study in the American University of Beirut Medical Center between 2001 and 2003 in Lebanon and reported that Gram-negative and Gram-positive organisms are responsible for 78.8% and 33.3% of infections, respectively. Baskaran et al. (2007) conducted a retrospective study at a university medical center in Malaysia and found that 60.3% of infections are caused by Gram-negative bacteria.

1.5 General approach to treatment

1.5.1 Granulocyte-colony stimulating factor (G-CSF)

In the 1960s, the discovery of colony-stimulating or myeloid growth factors was considered as a great achievement in the history of hematology and development of medical oncology practice. G-CSF stimulates the proliferation of neutrophils and accelerates their transport from the bone marrow to the blood pool. The development and release of neutrophils occur in three sites: in the bone marrow where cells develop from stem cells to mature, in the blood where neutrophils flow along with red blood cells and in infected tissues where neutrophils kill bacteria. The normal time for neutrophil production from the bone marrow to the blood pool is 6 days. D. C. Dale (2001) reported a 50% reduction in time (i.e., about 3–6 days) of

neutrophil maturation and release. Crawford *et al.* (2004) conducted randomized controlled trials and demonstrated that G-CSF considerably accelerates neutrophil recovery after chemotherapy (Aapro, Crawford, & Kamioner, 2010; Gerlier *et al.*, 2010).

The guidelines of the American Society of Clinical Oncology (ASCO), EORTC–IATG, European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN version 1.2013) for the use of G-CSF are based on risk factors. These factors include the type of chemotherapy and patient-related factors, such as age, performance status and comorbidities. Febrile neutropenia is categorized into three groups on the basis of risk factors, namely, low risk (<10%), intermediate risk (<10%–20%) and high risk (>20%). These guidelines recommend the use of G-CSF for patients with a high risk (>20%) of febrile neutropenia (Gerlier *et al.*, 2010).

1.5.2 Strategies of antimicrobial therapy

In the early 1960s, the incidence of neutropenia was accompanied by potent factors, such as degree and duration of neutropenia and overall risk of infection. Virulent Gram-negative organisms predominantly cause death and sepsis. However, a limited number of antibiotics were available to treat infections during that time. Aminoglycosides (AGs) were introduced in the 1970s; carbapenem, monobactams and quinolones were made available in the 1980s (Hathorn & Lyke, 1997; Sipsas *et al.*, 2005).

With the development of broad-spectrum β-lactam antibiotics 10 years ago, the effectivity of broad-spectrum antibiotic monotherapy in the treatment of febrile neutropenic patients has been extensively investigated. In theory, monotherapy provides several advantages over combination therapy; these advantages are reduced

toxicity and ease of administration. Nevertheless, monotherapy and combination therapy are characterized by several drawbacks, including inconsistencies in objectives and definitions of success and failure. Researchers have yet to provide evidence that supports monotherapy as the gold standard of empirical antibiotic therapy (Viscoli, 1998).

Combination therapy is the optimum treatment approach for febrile neutropenic patients. The combination of antibiotic regimens synergistically affects Gram-negative organisms. However, combination therapy provides several disadvantages, such as high cost and unpredictable pharmacodynamic antibiotic behavior (Viscoli, 1998).

Appropriate antimicrobial stewardship strategies are required to reduce the risk and consequences of febrile neutropenia (Lyman *et al.*, 2010). However, recommendations for the initial empirical antibiotic therapy for febrile neutropenia can be provided if clinicians are aware of local bacterial spectrum, susceptibility patterns and individual clinical situations (Hathorn & Lyke, 1997; Klastersky, 2004). No single antibiotic regimen is optimal. As such, changes in bacterial spectrum, resistance patterns and new therapeutic agent availability have led to the development of new options (K. V. Rolston, 1999).

The Infectious Disease Society of America (IDSA), ASCO, NCCN, Infectious Diseases Working Party of the German Society of Hematology and Oncology and Chemotherapy Society of Spain (SEQ) established clinical practice guidelines for the empirical initial antibiotic therapy (Table 1.1) for febrile neutropenic patients (Glasmacher *et al.*, 2005; Lyman & Rolston, 2010; Sipsas *et al.*, 2005).

Table 1.1 Recommendations for the empirical initial antibiotic therapy for febrile neutropenia

Guidelines	Monotherapy	Combination Therapy
IDSA (Infectious Disease Society of America)	Ceftazidime	Piperacillin–Tazobactam/Ticarcillin/Clavulanate + Aminoglycoside
	Cefepime	Aminoglycoside + Cefepime–Ceftazidime
	IC	Aminoglycoside + Imipenem–Cilastatin
	Meropenem	Aminoglycoside + Meropenem
	PT	
NCCN (National Comprehensive Cancer Network)	Ceftazidime	Aminoglycoside + Anti-pseudomonal penicillin
	Cefepime	Aminoglycoside + Extended-spectrum cephalosporin
	IC	Ciprofloxacin + Anti-pseudomonal penicillin
	Meropenem	Double β-Lactam
IHO (Infectious Diseases Working Party of the German Society of Hematology and Oncology)	PT	Aminoglycoside + Acylaminopenicillin
	Ceftazidime	Aminoglycoside + Third- or fourth-generation cephalosporin
	Cefepime	
	IC	
	Meropenem	
SEQ (Chemotherapy Society of Spain)	Cefepime	Not recommended for routine use
	Meropenem	
	PT	

IC: Imipenem–cilastatin, PT: Piperacillin–tazobactam

1.6 Outcome measurements

1.6.1 Evaluation of response

Primary outcome included treatment success without modification or addition of other antibiotics to initial treatment regimen within 72 h of therapy. The response to therapy was assessed after 72 h of therapy (Frank, Mutter, Schmidt-Eisenlohr, & Daschner, 2003; Freifeld *et al.*, 2011; Harter *et al.*, 2006; Oztoprak *et al.*, 2010; Rossini *et al.*, 2005).

1.6.2 Effectiveness of therapy

The effectiveness of therapy was defined on the basis of the following endpoints: (1) complete resolution of fever (reduction in temperature to <38 °C measured orally and sustained for 48 h); (2) complete disappearance of clinical signs and symptoms of infection (clinical deterioration and progression of presumed infection); and (3)

bacteriological response of eradication of infectious organisms without changes in the initially assigned therapy (Frank *et al.*, 2003; Freifeld *et al.*, 2011; Harter *et al.*, 2006; Oztoprak *et al.*, 2010; Rossini *et al.*, 2005).

1.6.3 Failure of therapy

The failure of therapy was evaluated on the basis of the following endpoints: (1) when antimicrobial therapy was modified by adding other antibiotics or discontinuing the initial empirical therapy and initiating other new antibiotics for 72 h of treatment; (2) persistent fever in a patient with signs of clinical deterioration, microbiological evidence and clinical progression of the presumed infection or adverse event associated with the antibiotic regimen; and (3) deaths occurring within 72 h of treatment (Freifeld *et al.*, 2011; Harter *et al.*, 2006; Hess, Böhme, Rey, & Senn, 1998; Oztoprak *et al.*, 2010).

1.6.4 Toxicities

The safety of therapy was evaluated by monitoring laboratory values. Nephrotoxicity and hepatotoxicity, which are characterized by an increase in serum creatinine, transaminases, bilirubin or alkaline phosphatase by at least twice the upper normal limit, were examined through laboratory analysis (Harter *et al.*, 2006; Raad, Abi-Said, Rolston, Karl, & Bodey, 1998). Hypokalemia is defined as an increase in serum potassium level of >10 mmol below the lower limit of the normal range (Ariffin *et al.*, 2001).

1.6.5 Overall improvement

Overall improvement was assessed after 7 days (Frank *et al.*, 2003; Freifeld *et al.*, 2011; Harter *et al.*, 2006; Oztoprak *et al.*, 2010; Rossini *et al.*, 2005).

1.7 Global incidence of neutropenia

The risk of infection is at its maximum when neutrophil count is <500 cells/mm^3 (Hsieh, Everhart, Byrd-Holt, Tisdale, & Rodgers, 2007). The normal level of neutrophils in human blood varies with age, race and ethnicity (Frey, 1999). Grann *et al.* (2008) surveyed 261 populations of six ethnic groups from the Caribbean and the US and evaluated the association between the country of origin and the normal WBC and ANC levels. This survey revealed that populations of African and Caribbean descents more likely possess lower WBC counts and ANCs than those of Caucasians and Dominicans. According to the National Health and Nutritional Examination Survey from 1999 to 2004, the prevalence of neutropenia varies with age, gender and ethnicity. The prevalence rates of neutropenia are 4.5%, 0.79% and 0.38% in African–American, Caucasian and Mexican–American participants, respectively. Among these ethnic groups, 6.65% of African–American males and 3.57% of African–American females are likely neutropenic; by contrast, 0.90% of Caucasian males and 0.59% of Caucasian females and 0.57% of Mexican–American males and 0.39% of Mexican–American females are neutropenic (Hsieh *et al.*, 2007).

The reference range of neutrophil count in Arabs has not been established. Studies have proposed that the Arab population possesses lower neutrophil counts than other ethnic groups do (Europeans and Mexicans). These Arab populations live in tribes and practice endogamy; thus, genetic conditions are altered (Denic *et al.*, 2009). Denic and Nicholls (2011) conducted a survey at Al Ain Hospital, United Arab Emirates and found that the mean neutrophil count in Arabs is lower than that in European populations. In the past three decades, benign neutropenia was commonly observed among Jordanians, Kuwaitis and Palestinians. More than 30% of the

Omani Arab population presents abnormal neutrophil levels (Al-Ankoodi & Rawther, 2004). Al-Qahtani (2008) found that 90.7% of Saudi Arabian populations exhibited mild neutropenia and 9.3% presented with moderate neutropenia between 1995 and 2006 at the King Khaled University Hospital, Saudi Arabia.

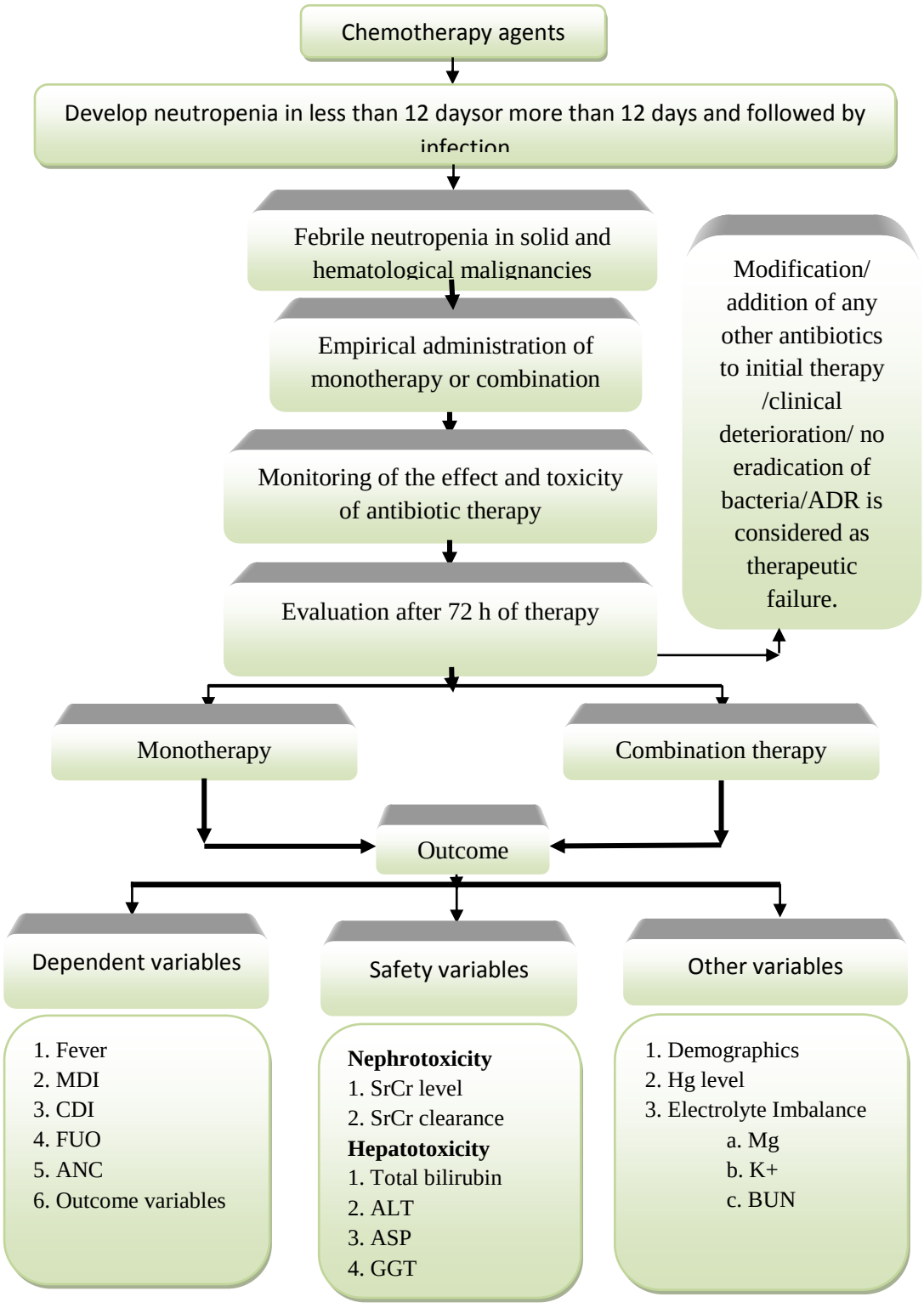
1.8 Conceptual framework

Febrile neutropenia is induced by combination therapy and monotherapy of cytotoxic drugs in cancer patients. The intensity of chemotherapeutic agents is a risk factor of neutropenia development (Lyman *et al.*, 2005; Lyman & Rolston, 2010). Neutropenia can be complicated by bacterial infections. Bacterial etiology has shifted from Gram-positive organisms to Gram-negative organisms (Baskaran, Gan, Adeeba, & Sam, 2007; Burney, Siddiqui, Farooqui, & Khurshid, 1998; Eltahawy, 2003; Bassam Abdul Rasool Hassan, Yusoff, & Othman, 2011; Kanafani *et al.*, 2007; D Yadegarynia, Tarrand, Raad, & Rolston, 2003). Regional and climatic conditions also influence the changes in bacterial etiology (Hathorn & Lyke, 1997; Wingard, 2011). Considering these findings, we provide a precise guide on the selection of a first-line empirical antimicrobial therapy in the management of infections in febrile neutropenic episodes. This study also emphasizes the optimal selection of combination therapy for the broad-spectrum coverage and synergistic effect of antibiotics.

This study aims to survey the dependent variables of the effectiveness and safety of antibiotic use in febrile neutropenic cancer patients. Despite the effectiveness of antibiotics, certain antibiotics are characterized by several drawbacks, such as nephrotoxicity and hepatotoxicity (Hathorn & Lyke, 1997). Our study also highlights the predictor variables of the effectiveness and toxicity of antibiotics in febrile neutropenic cancer patients.

Our conceptual framework is categorized as the initial development of febrile neutropenia after patients receive chemotherapeutic agents and manifest infection. This study is divided into the following three stages. Stage 1 and Figure 1.1 summarize the development of neutropenia and selection of effectiveness, safety and outcome variables for the success of empirical monotherapy and combination antibiotic therapy in febrile neutropenia with solid tumor and hematological malignancies. Stage 2 and Figure 1.2 represent the assessment of the effectiveness, safety and outcome variables for the success of monotherapy or combination therapy. Stage 3 and Figure 1.3 present a comparison between monotherapy and combination antibiotic therapy in terms of success and failure of initial therapy.

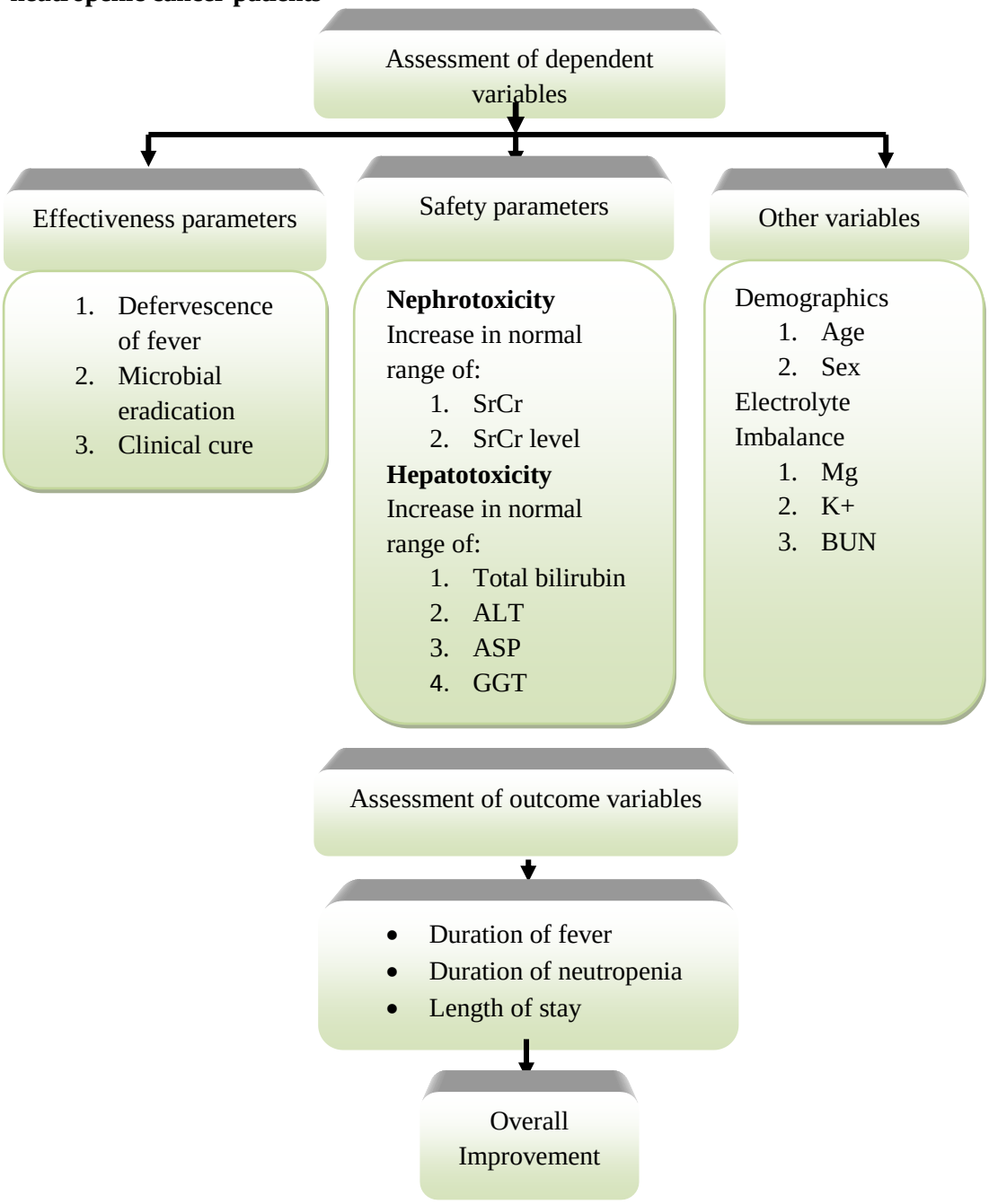
Stage 1. Development of febrile neutropenia, evaluation of effectiveness and safety and outcome variable



ALT: Alanine transaminase. ALP: Alkaline phosphatase. ANC: Absolute neutrophil count. ADR: Adverse drug reaction, BUN: Blood urea nitrogen. CDI: Clinically defined infection. FUO: Fever of unknown origin. GGT: Gamma glutamyl transferase. Hg: Hemoglobulin. K^+: Potassium. MDI: Microbiologically defined infection. Mg: Magnesium. SrCr: Serum creatinine.

Figure 1.1 Conceptual framework for the selection of monotherapy or combination therapy and its effectiveness, safety and other influencing variables

Stage 2. Assessment of the effectiveness and safety of antibiotics in febrile neutropenic cancer patients



ALT: Alanine transaminase. ASP: Alkaline phosphatase. BUN: Blood urea nitrogen. GGT: Gamma glutamyl transferase. K^+: Potassium. SrCr: Serum creatinine. Mg: Magnesium.

Figure 1.2 Assessments of initial antibiotic therapy in terms of effectiveness, safety and overall improvement

Stage 3 **Comparison of monotherapy versus combination therapy in terms of effectiveness, safety, outcome variables and overall improvement**

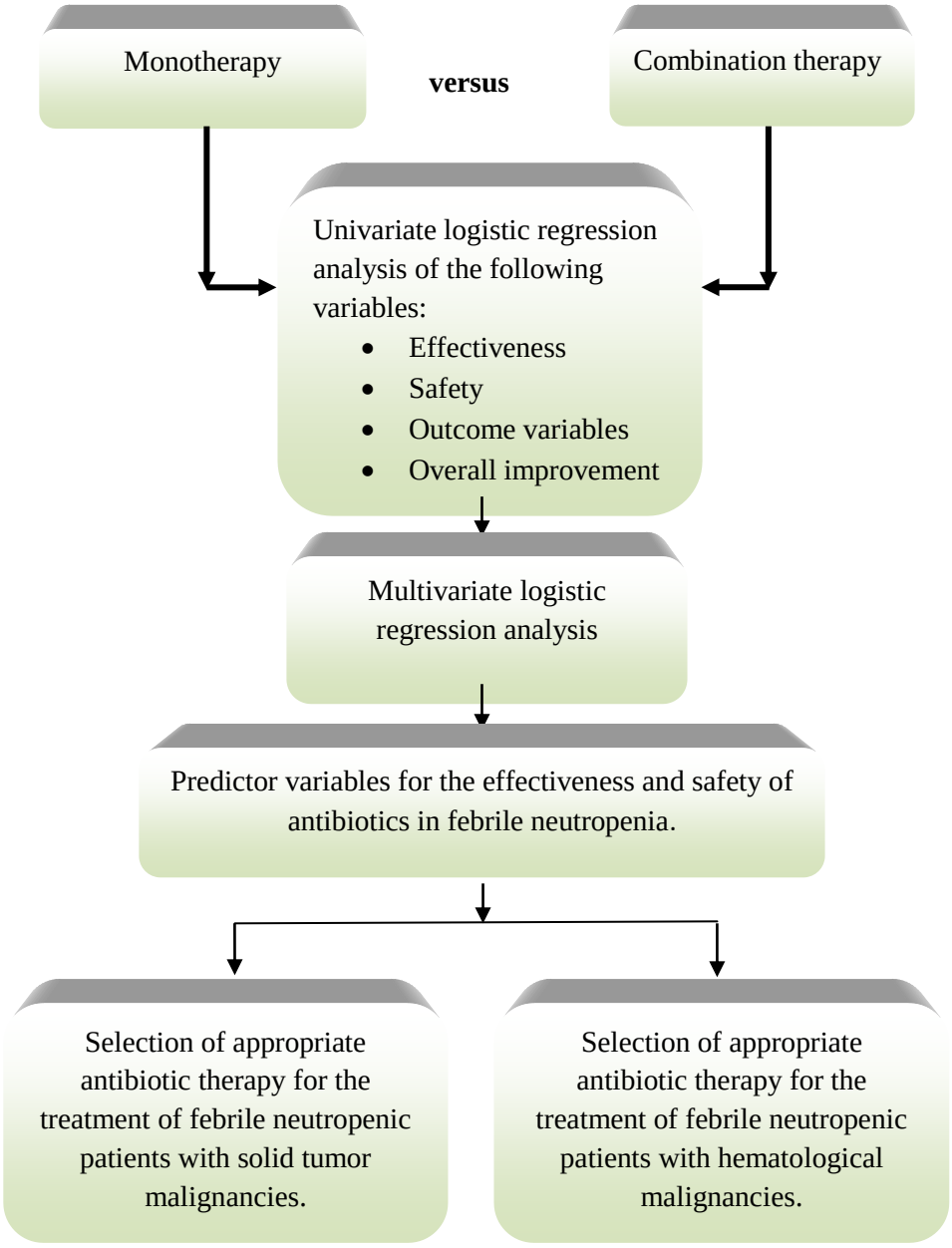


Figure 1.3 Logistic univariate and multivariate regression analyses of monotherapy versus combination therapy