PROSPECTIVE STUDY OF OUTCOMES OF HIGH RISK FEBRILE NEUTROPENIA IN PATIENTS OF ACUTE LEUKEMIA - CLINICAL AND MICROBIOLOGICAL ASPECTS

This dissertation is submitted to

THE TAMILNADU

DR MGR MEDICAL UNIVERSITY

In partial fulfillment of the University for

D.M (MEDICAL ONCOLOGY)

DEGREE EXAMINATION OF AUGUST 2012

COLLEGE OF ONCOLOGICAL SCIENCES

CANCER INSTITUTE (WIA)

ADYAR

CHENNAI – 600 020

August 2012

CERTIFICATE

This is to certify that this dissertation on **"Prospective study of Outcomes of High Risk Febrile Neutropenia in patients of Acute Leukemia – Clinical and Microbiological aspects",** is a bonafide work done by Dr Vignesh Kanda Kumar.B, in the Department of medical Oncology, College of Oncological Sciences, Adyar, Chennai, under my overall supervision and guidance.

Place : Chennai

Date :

Dr T G Sagar MD , DM

Professor and Head

Department of Medical Oncology

College of Oncological Sciences

Adyar , Chennai - 600020

ACKNOWLEDGEMENT

Words are inadequate to express my gratitude, towards each and everyone, who has been a guiding force and inspiration for me in making this dissertation, without whom all this effort would have never seen the light of the day.

I humbly wish to place on record my deep sense of gratitude to **Dr T G Sagar, MD , DM**, Director Cancer Institute(WIA), Adyar, Chennai, Professor and Head , Chairman , Division of Medical Oncology, who with his profound knowledge and experience gave me constant support, encouragement and guidance during the entire part of this study.

I express my sincere thanks to **Dr Rejiv Rajendranath MD,DM,DNB**, Associate Professor, Department of Medical Oncology for all his valuable guidance, constant encouragement and meticulous correction of my dissertation work.

At this juncture, it gives me great pleasure to express my earnest gratitude to Dr **Prasanth Ganesan MD,DM**, Assistant professor for his valuable guidance, constructive suggestions and constant motivation.

I would like to thank Mrs. **Varalakshmi Msc,** Head of Department of Microbiology, Cancer Institute Adyar, for her constant support and inputs in making this study .

I also owe my sincere thanks to **Dr Krishna Rathinam MD,DM** Professor of Medical Oncology and **Dr V Srinivasan MD** for being a constant source of encouragement. I thank all my teachers within and outside the Institute, without whom I am not , what I am today.

I am extremely grateful to my fellow colleagues for all constructive suggestions.

I also extend my respect and gratitude to my father. I would like to thank my wife for her constant support all through my post graduate career

My acknowledgement will be incomplete if I do not mention about the Late **Dr Krishnamurthy** , advisor and **Dr V Shanta** Executive Chairman of Cancer Institute (WIA), whom I have always admired and drawn inspiration from, and whose blessings I will seek throughout my endeavor, in this field of Medical Oncology.

CONTENTS

INTRODUCTION

Treatment and outcome of hematological malignancies has improved during recent decades due to improved supportive care and availability of modern effective drugs and regimens. However infectious complications with or without bleeding is the direct cause of death in about 50%-80% of patients dying with acute leukemia.[1-5] As early as 1845, infection was recognized as an important complication of leukemia. Neutropenia is the primary chemotherapy induced immune defect, rendering patients susceptible to infections. The incidence and severity of infection in neutropenic patients are inversely proportional to the absolute neutrophil count (ANC) and to the duration of neutropenia.[6] Importance of neutropenia as a predisposing factor for infection was clearly recognized after effective therapeutic agents became available.

The most important factor limiting the planned intensity of antineoplastic therapy is febrile neutropenia. Besides neutropenia there are several other factors that influence the risk of developing infections like intensity and phase of chemotherapy regimen, indwelling catheters, endemicity of the pathogenic organisms and duration of hospital stay. Normal human skin and mucosal colonization change during chemotherapy and hospitalization. Chemotherapy induced mucositis often occurs throughout the

gastrointestinal tract, facilitating spread of endogenous flora to the blood circulation leading to febrile neutropenia. The pattern of fever in the presence of neutropenia is non specific and not pathognomic of any type of infection or non infectious process and can be suppressed by the antipyretic effect of drugs such as corticosteroids. Compelling delays in treatment or reduced dosage due to febrile neutropenia compromises effectiveness of antineoplastic therapies with potential implications.[7]

Central venous catheters (CVCs) have improved the management of patients with hematological malignancies by facilitating chemotherapy administration, supportive therapy and blood sampling. Organisms causing CVC- related infection can gain access to the device through: contamination of catheter hub, hematogenous spread from a distant site of infection, invasion of the skin insertion site or infusion of contaminated fluid through the device. Antibiotic therapy for catheter-related infection is often initiated empirically. The initial choice of antibiotics will depend on the patient's general condition, comorbid illness, the risk factors for infection, and the likely pathogens associated with the specific intravascular device.

Rapid development of bacterial resistance and emergence of new clinical problems related to new treatment modalities complicates specific approach to infection management. Epidemiology of pathogens is dynamic

and contemporary local data is extremely important for therapeutic decisions. Periodically appraising the distribution of pathogens responsible for infection in neutropenic patients is highly essential. Identifying patients with a low risk of acquiring serious infection is essential as they can be managed on outpatient basis. High risk neutropenia on the other hand, as in acute leukemia requires inpatient treatment in almost all cases.

Indian data on high risk febrile neutropenia in acute leukemia is limited. Since local data is essential to guide therapeutic decisions, a prospective study was conducted to generate data for updating our clinical practice.

AIMS AND OBJECTIVES

- To study the clinical features, risk factors, microbiological aspects and outcome of high risk febrile neutropenia in acute leukemia patients treated at the medical oncology department.
- To study the profile of catheter related infections (CRI) in the above patients
- To determine factors influencing the outcome of high risk febrile neutropenia

REVIEW OF LITERATURE

Febrile neutropenia is an oncological emergency that is associated with substantial morbidity, mortality and cost.

Infections in neutropenic acute leukemia patients:

Until 1948, there was no specific treatment for acute leukemia.[8] As there was very little to do for the natural course of the disease, there was no major interest to study or understand the possibility of infectious complications. Neutropenia is a common consequence of acute leukemia but its role in infection was not fully recognized till the early 1960's.[9] Both malignancy and therapy employed to manage it contributes to immune compromised state of acute leukemias.

30%-60% of neutropenic patients develop an infection, of whom 13-37% develop bacteremia.[10-13] During the last three decades the mortality rate due to infections in neutropenic patients has decreased from 21% to 7%.[14] The risk of severe infection is high at absolute neutrophil count of $<0.1x10^9/L$.[15]

Hosts inflammatory responses are altered by neutropenia and masks the classical signs and symptoms, often leading to difficulty in detecting the focus of infection.[16] However mononuclear cells including fixed tissue macrophages produce endogenous pyrogen (IL-1) and these mononuclear cells persist after chemotherapy explaining the presence of fever in neutropenic patients despite poor inflammatory response.[17] Fever the principal sign of infection is often the only evidence of infection in neutropenic patient.

Spectrum of microbial pathogens in acute leukemia:

There has been a significant change in the spectrum of infections in acute leukemia patients with neutropenia. In 1950's and 1960's Staphylococcus aureus was the predominant isolate in neutropenic patients.[5] Gram negative bacilli including Escherichia coli, Klebsiella species and Pseudomonas aeroginosa became the most frequent isolate with the introduction of beta-lactamase resistant antistaphylococcal penicillins.

Several studies conducted after 1980's revealed a shift in the etiology of bacterial infections from a predominance of gram negative pathogens to gram positive cocci. Studies conducted by the International Antimicrobial Therapy Cooperative Group have documented a shift in the pattern of pathogens. By the end of 20th century, gram positive cocci was responsible for 60%-70% of bacteremia episodes .[18-21]

Some of the factors responsible for this shift include use of intensive chemotherapy toxic to the upper and lower gastrointestinal mucosa, fluroquinolone prophylaxis that suppress aerobic gram negative bacilli colonizing the gastrointestinal tract, profound and prolonged neutropenia, use of H_2blockers which reduce gastric pH and promote overgrowth of oropharyngeal gram positive microflora and the widespread use of indwelling central venous access devices.[22] Common gram positive organisms implicated in febrile neutropenia include Viridans group Streptococci, coagulase negative Staphylococci and the Enterococcus species. Enterococcus species have emerged as virulent pathogens due to acquisition of antibiotic resistant plasmids.

Anerobes are responsible for mixed infections in peri anal region and mouth but play minimal role in primary infections of neutropenic patients with fever. Fungi are the major culprits in patients with prolonged neutropenia and who receive antibiotics for protracted course.[23] The common fungal pathogens are Candida species and Aspergillus species. Virus or Parasites can cause secondary as well as primary infections.

Recently there are indications that the etiological pattern of pathogens that cause bacteremia is changing again, with gram negative bacilli starting to predominate again. In a retrospective study from Malaysia, gram negative

bacteremia was present in 35.5% of patients with acute leukemia. Gram positive bacteremia incidence in leukemia group was 27.6%.[24] Enterobacteria was the most frequently isolated gram negative bacillus. The most frequently isolated gram positive organism was coagulase negative Staphlococci. In a study from Lebanon, 177 episodes of neutropenic fever was prospectively observed. Leukemia constituted majority of underlying malignancy. Positive blood cultures were documented in 18.6% episodes of neutropenic fever. The rate of gram negative blood stream infections exceeded that of gram positive blood stream infection (14.7% vs 6.2%).

Initial evaluation of febrile neutropenia patients:

Pretreatment evaluation of patient should be as thorough as possible. In a neutropenic patient undetected and untreated infection can be rapidly fatal. Careful history and a detailed examination to look for subtle signs of inflammation are necessary. Even subtle evidence of inflammation must be considered as a sign of infection.

Careful attention should be paid for frequent foci of infection such as vascular catheters, oropharynx, lung, paranasal sinuses, perineum. Even minimal erythema and serous discharge at central venous catheter exit site should be considered significant in a neutropenic patient. Minimal perianal erythema and tenderness can rapidly progress to perianal cellulitis. In a

retrospective study from Malaysia on bacteremia in patients with febrile neutropenia the infective foci was analysed. In majority of the febrile episodes, infective could not be identified (29.3%). Central venous catheter (CVC)'s contributed 23.3% of infective foci source followed by respiratory tract (13.8%). The gastrointestinal tract and perianal region were the infective foci in 6.9% individually.

Culture of urine sample is indicated if signs or symptoms of urinary tract infection exist, a urinary catheter is in place, or the findings of urine analysis are abnormal.[25] A baseline radiograph is helpful in patients who later develop respiratory symptoms or evidence of an infiltrate; however a chest radiograph is usually recommended for only those with signs and symptoms of pulmonary infection.

Catheter related infections:

Catheter-related infections (CRI) cause considerable morbidity in leukemic patients while undergoing intense chemotherapy protocols. The cornerstone in the diagnosis of CRI's are the positive blood cultures, while local signs of infection are not necessarily present. Both peripheral blood and blood from the vascular catheter should be sent for culture. The diagnosis of a CRI is supported by a shorter time to positivity of catheter blood cultures as compared with peripheral blood cultures.

A definite diagnosis may require catheter removal and microbiological analysis in many of the cases. Primary removal of the catheter is mandatory in Staph aureus and Candida infections, as well as in case of tunnel or pocket infections.

Diagnosis Criteria for catheter related infections:

Definite CRI :

Pathogen detected at the catheter tip by a standard method plus same pathogen with the same susceptibility pattern detected in blood culture or pathogen detected in quantitative catheter and peripheral blood cultures with a catheter colony forming unit (CFU) to peripheral CFU ratio ≥10.

Probable CRI:

Local infection at the insertion site coupled with positive blood culture or remission of previously refractory fever within 48 h after catheter removal plus positive blood culture.

Possible CRI :

Pathogen detected in blood culture that is typically implicated in causing catheter infections or positive blood culture and no other focus identified in a patient with an indwelling CVC.

The most commonly isolated agent of catheter-related bacteremia was coagulase negative staphylococci. Staphylococcus aureus, enterococci, gram negative bacteria (Pseudomonas aeruginosa, Acinetobacter baumannii), and Candida species are frequently detected as well.[26-28] Femoral vein should be avoided as a site for CVC insertion due to the high microbial colonization rate in adults[29] and the higher risk of developing deep vein thrombosis.[30]

Chlorhexidine solutions should be prefered to aqueous povidone iodine solutions for catheter insertion and changing dressings.[31-33] Systemic prophylactic antibiotic treatment prior to insertion of the catheter does not result in a significant reduction of CRI.[34-35] Topical application of antibiotic ointments for reducing staphylococcal colonization at the catheter insertion site is not advisable due to the risk of selection of resistant bacteria and fungi.[36] Sterile gauze and transparent film can be used for covering the CVC insertion site. Sterile gauze should be changed every 2 days and transparent film once a week unless local contamination or local signs of inflammation are present.[37] Presently the use of impregnated catheters cannot be generally recommended as only one randomized trial in cancer patients had shown reduction in catheter related blood stream infections.

In a prospective study in 103 ICU's in Michigan, five evidence based procedures namely hand washing, cleaning skin with chlorhexidine, using full

barrier precautions during the insertion of central venous catheters, removing unnecessary catheters and avoiding femoral site were strictly implemented for a study period of 18 months. At the end of 3 months of implementation of these measurses, rate of CRI per 1000 catheter-days reduced from 2.7 at baseline to 0[38]. The 66% reduction in CRI was maintained throughout the study period.

Risk assessment in febrile neutropenia:

Neutropenia is the most important risk factor. There is increased risk of infection with ANC <500/ml and an ANC less than 100/ml has the highest risk. Patients whose granulocyte counts recover in less than 1 week have low risk of complications following onset of fever. Patient's who have prolonged neutropenia, practically defined as more than 7 days have high risk of complications. A risk assessment model for outcome was developed using clinical variables by Talcott et al [39] and later validated in a study of 444 cancer patients. The 3 clinical risk criteria in this study were: prior inpatient status, serious independent co morbidity, and uncontrolled cancer. Patient's who does not have any of the risk factor were considered low risk. 34% of patients with risk factors developed serious medical complications compared with 5% incidence in the low risk group.

An internationally validated scoring system to identify low risk febrile neutropenia cancer patients has been developed by the Multinational Association for Supportive Care in Cancer [40] (MASCC) which included 1351 patients. A MASCC risk index score of 21 or more points identified low risk patients with a sensitivity of 71%, specificity of 68% and positive predictive value of 91% (Table.1).

Table1. MASCC risk stratification for febrile neutropenia

Characteristics	Weight
No or mild symptoms	5
Moderate symptoms	3
No hypotension	4
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Outpatient status	3
Age less than 60 years	2

Although the MASCC risk index is frequently used to stratify patients, it is focused on the detection of low-risk febrile neutropenic patients. FN associated with hematological malignancies has features that are different from FN associated with malignant solid neoplasms. No generally accepted

predictive model exclusively for high-risk febrile neutropenic patients, especially with hematologic malignancies, has been developed.

Initial management of febrile neutropenia:

Empirical antibiotics has to be initiated promptly in febrile neutropenic patients. The mortality from gram negative infections approached 80% if there was delay in initiation of empirical antibiotics.[41] The first effective treatment for febrile neutropenia was demonstrated by Schimpff and consisted empiric therapy of a combination of carbenicillin and gentamycin.[42] There are various guidelines available for choice of empirical therapy.

NCCN[43] guidelines offers i) monotherapy with a carbapenem or an extended spectrum antipseudomonal penicillin. ii) aminoglycoside with either an antipseudomonal penicillin or antipsedomonal cephalosporin iii) ciprofloxacin with an antipsedomonal penicillin. Infectious Disease Society of America (IDSA)[44] recommendation 2010 for high risk febrile neutropenia requiring admission and empirical therapy are monotherapy with an antipseudomonal beta-lactam agent, such as cefepime, a carbapenem or piperacillin-tazobactam. Other antimicrobials like aminoglycosides, fluoroquinolones, and / or vancomycin may be added to the initial regimen for management of complications like hypotension or pneumonia or if antimicrobial resistance is suspected or proven.

Vancomycin is not recommended as a standard part of the initial antibiotic regimen for febrile neutropenia and is discouraged. The clinical indications for vancomycin or other agents active against aerobic gram positive cocci includes suspected catheter-related infection, mucositis, skin or soft-tissue infection, pneumonia, or hemodynamic instability. Penicillin-allergic patients usually tolerate cephalosporins, however those with a history of an immediate-type hypersensitivity reaction should be treated with a combination that avoids beta-lactams and carbapenems, such as ciprofloxacin plus clindamycin or aztreonam plus vancomycin.[44]

Empirical and preemptive antifungal therapy:

Empirical antifungal therapy refers to initiation of an antifungal agent at the first possible clinical evidence of fungal infection, which is usually persistent or recrudescent fever on or after day 4 of empirical antibiotic therapy.[45] Candida species are colonizers of mucosal surfaces and may cause bloodstream infection with mucosal barrier breakdown .[46-47] In two small randomized studies in the 1980s empirical amphotericin B reduced the risk of invasive fungal infection by 50– 80% and the risk of fungal infection related mortality by 23-45%. Lipid formulations of amphotericin B that improve the therapeutic ratio of the traditional formulation are : amphotericin B in lipid complex (ABCL), amphotericin B colloid dispersion (ABCD), liposomal amphotericin B . The safety and efficacy of these formulations is well

established. These formulations have comparable efficacy and are less nephrotoxic than conventional amphotericin.

An open labeled randomized study with a non inferiority design compared voriconazole to a lipid preparation of amphotericin B in the empirical treatment of febrile neutropenia. The overall success rate was 30.6% with liposomal amphotericin B and 26% with voriconazole. [48] In a recent trial comparing voriconazole with amphotericin B in documented invasive Aspergillus infection, voriconazole was associated with a response rate of 52.8 Vs 31.6% for amphotericin B.[49] Empiric voriconazole was associated with greatest benefit in relapsed acute leukemia and allogenic stem cell transplantation.

Preemptive antifungal therapy refers to treatment of only those patients with additional findings suggestive of invasive fungal infection, such as serologic test results or chest CT findings. Macronodules with or without a halo sign are the most typical findings associated with invasive aspergillosis on computed tomography(CT) chest. The halo sign represents edema or blood surrounding the nodule. [51-53] Preemptive initiation of antifungal therapy directed against Aspergillus on the basis of finding a halo sign has been associated with improved survival.[54-55]

As per IDSA[44] recommendation 2010 preemptive antifungal therapy currently remains largely experimental and is not standard of practice.

Diagnosis of invasive fungal infection:

Two serum fungal diagnostic tests, the D glucan test and the galactomannan test, may aid in the detection of common invasive fungal infections and is recommended only for high risk patients.

The D glucan test detects most of the relevant fungal pathogens, including Candida species, Aspergillus species, Pneumocystis species, and Fusarium species where as the galactomannan assay detects only Aspergillus species and Penicillium species, and does not detect other pathogenic fungi. The galactomannan test should be used only for patients at risk for Aspergillus infection.The European Organization for Research and Treatment of Cancer and Infectious Disease Mycoses Study Group (EORTC/MSG) guidelines criteria[56] for diagnosis of invasive fungal disease (IFD) is shown in Table 2 and Table 3 shows criteria for possible and probable IFD.

Table 2: Criteria for diagnosis of proven IFD

Specimen and analysis	Moulds	Yeasts
Microscopy: sterile material	Histopathologic, cytologic or direct microscopic demonstration of hyphae and tissue damage from needle aspiration/ biopsy specimen.	Histopathologic, cytologic or direct microscopic demonstration of yeasts from normally sterile site (other than mucous membrane)in needle aspiration/ biopsy specimen
Culture: sterile site	Recovery of mould from normally sterile but clinico-radiologically abnormal site (excluding BAL fluid, sinus cavity specimen and urine)	Recovery of yeast from normally sterile but clinico-radiologically abnormal site
Culture: blood	Recovery of mould (eg:Fusarium) in the context of a compatible disease process*	Blood culture yielding yeast
Serology: CSF	Not applicable	Cryptococcal antigen in CSF

*Recovery of Aspergillus from blood denotes contamination

Table 3: Criteria for diagnosis of possible/probable IFD

Factors	Criteria
Host factors	1. Recent history of neutropenia (< 500 neutrophils /µl for > 10 days) temporally related to the onset of fungal disease 2. Recepient of an allogenic stem cell transplant 3. Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/ kg/ day of prednisone equivalent for >3weeks. 4. Treatment with other recognized T cell immunosuppressants such as cyclosporine, TNF-alpha blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days. 5. Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)
Clinical criteria	
Lower respiratory tract fungal disease	Presence of one of the following 3 signs on CT: 1. Dense, well circumscribed lesion(s) ± halo sign 2. Air – crescent sign 3. Cavity

Sinonasal infection	Imaging showing sinusitis plus at least one of the following 3 signs: 1. Acute localized pain 2. Nasal ulcer with black eschar 3. Erosion of bony barriers
CNS infection	one of the following 2 signs: 1. Focal lesions on imaging 2. Meningeal enhancement on MRI or CT
Mycological criteria	Direct tests (cytology, direct microscopy, or culture)- Mould in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by one of the following: 1. Presence of fungal elements indicating a mould. 2. Recovery by culture of a mould (eg., Aspergillus, Fusarium, Zygomycetes) Indirect tests (detection of antigen or cell-wall constituents) 1. Aspergillosis – Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid or CSF 2. Invasive fungal disease other than cryptococcosis and zygomycoses –βeta D glucan detected in serum.

Invasive Aspergillosis:

In a randomized trial for invasive aspergillosis (IA), voriconazole was more effective than amphotericin B (53% vs 32% complete or partial response), and was associated with improved survival at 3 months.[49] In a retrospective analysis of patients with central nervous system (CNS) aspergillosis treated with voriconazole, 35% had complete or partial response which was much higher than historical controls treated with amphotericin B.[57] Initial monotherapy with caspofungin for IA has not yet been evaluated. In a study of 83 patients with Caspofungin as salvage therapy for IA response rate of 45% was achieved.[58]

Environmental precautions for febrile neutropenia patients:

The most effective way of preventing transmission of infection in the hospital is strict hand hygiene. Infection-specific isolation should be used for patients with symptoms or certain signs and standard barrier precautions should be followed. Fresh or dried flowers and plants should not be permitted inside the room of neutropenic patients.[43]

Antibiotic prophylaxis:

In a meta-analysis of 17 placebo-controlled trials of fluoroquinolone prophylaxis a relative risk reduction of 48% and 62% in all-cause mortality

and infection-related mortality respectively among fluoroquinolone recipients was demonstrated. Majority of patients included in this meta analysis had high risk hematologic malignancies with > 7 days of febrile neutropenia.[59] In a prospective randomized placebo-controlled trial performed by Bucaneve et al among patients expected to have ANC counts <100 cells/mm3 for >7 days, there was significantly reduced number of episodes of fever and the number of documented gram-negative bacillary infections.[60] There are no standardized clinical trials that have assessed the risk-benefit ratio of fluoroquinolone prophylaxis in children, however it may be considered in very high-risk situations. The cause of concern for fluoroquinolone based chemoprophylaxis is the potential for bacterial resistance and moreover it is not yet clear of when to start and discontinue prophylactic antibiotics.

National Comprehensive Cancer Network (NCCN) guidelines and the updated American Society for Blood and Marrow Transplantation (ASBMT)[61] guidelines recommends antibacterial chemoprophylaxis for high-risk patients. IDSA 2010 as well recommends fluoroquinolone prophylaxis for high-risk patients with expected ANC <100 cells/mm3 for >7 days. However the Centers for Disease Control and Prevention and the guidelines from professional societies in Japan and Germany does not recommend routine use of antibiotic prophylaxis for neutropenic fever.[43]

Antifungal prophylaxis:

In acute leukemia and autologous- hematopoietic stem cell transplantation (HSCT) recipients, fluconazole decreased fungal colonization, invasive fungal infection(IFI) and IFI related mortality.[62] The benefit was highest in autologous-HSCT patients who did not receive G-CSF and acute leukemia patients receiving cytarabine and anthracycline based mucotoxic regimens. Low dose amphotericin B and itraconazole did not provide survival benefit when compared to fluconazole. In neutropenic allogenic-HSCT recipients, randomized trials have shown that fluconazole prophylaxis controlled invasive candidiasis and yeast colonization. In a randomized study that included serum galactomannan surveillance with patients of allo-HSCT recipients, voriconazole was compared to fluconazole.[63] No difference was found in 180-day fungus free survival but a trend towards reduced IA was seen in voriconazole arm. Posaconazole was compared to fluconazole and itraconazole in a randomized study in myelodysplastic syndrome (MDS) and AML patients receiving induction or re induction and led to better protection from IFI and survival.[64]

Antiviral prophylaxis:

Prophylaxis with acyclovir is recommended for herpes simplex virus (HSV) sero positive patients undergoing acute leukemia induction or

autologous HSCT recipients at high risk for mucositis or allogenic HSCT recipients. Acyclovir prophylaxis for varicella zoster virus (VZV) is recommended for autologous HSCT and allogenic HSCT recipients (12 months) . Acyclovir should be given as cytomegalo virus(CMV) prophylaxis for allogenic HSCT recipients under close surveillance and pre emptive therapy should be instituted if required.[43]

Granulocyte colony stimulating factor (G-CSF):

NCCN and ASCO have issued guidelines for G-CSF use in neutropenic patients. G-CSF in general is used for neutropenic patients with severe infection like IFI, pneumonia, progressive infection, uncontrolled primary disease, age greater than 65 years, prolonged and profound neutropenia.[65-66]

Indian data on febrile neutropenia:

Indian data on febrile neutropenia in acute leukemia is limited with most of the studies being retrospective and few prospective studies. A prospective study of infectious complications in children and young adults with acute lymphoblastic leukemia was conducted at Cancer Institute (WIA), Adyar, Chennai over a study period of 22 months by Santa et al.[67] The number of febrile episodes encountered in induction were 166 .Infection was documented in 62 episodes(37.3%) of which gram negative was 37.15%, gram positive 22.6%, and fungal 40.3%. 147 episodes of fever were documented in

consolidation and infection was documented in 44 episodes (30%). Microbiological spectrum revealed gram negative 45.5%, gram positive 34.1% and fungal infections 20.4%. Growth factors were required in 30.6%. The infective foci could not be identified in majority of patients. Majority of infections were bacterial and gram negative organisms predominated over gram positive organisms. Tropical infections like malaria, tuberculosis and scabies were also reported in that study.

In a retrospective analysis of 75 patients with acute myeloid leukemia treated at AIIMS, Delhi from January 1984 to December 1988 by Kumar et al[68] 184 febrile episodes were documented. 31 episodes of fever (16.84%) were non neutropenic whereas 153 episodes (83.15%) were neutopenic fever. Among patients with febrile neutropenia, microbiologically documented infection was seen in 58.2% . The sites of infection were: chest (37.9%), sepsis (13.72%), upper respiratory tract (13.7%), skin and soft tissues (7.8%), genitourinary (7.2%), gastrointestinal tract (5.2%), and disseminated fungal infections (2.6%). Microbiologically, gram negative organisms were common, followed by gram positive organisms.

In a report of 53 children with acute lymphoblastic leukemia with age range between 5 months to 11 yrs, 68 febrile episodes were investigated. Only 24 febrile episodes had ANC < 500/mm^3. In 33 episodes microbial organisms

were reported. In 27 episodes bacteremia was identified. The commonest isolate was Escherichia coli (18.6%), followed by Staphylococcus aureus (15.2%), Klebsiella pneumoniae (10.2%), coagulase negative Staphylococcus (10.2%), Acinetobactor (8.5%), Pseudomonas aeruginosa (8.5%), and Clostridium species in three patients.[69] Pneumonia and diarrhea occurred in 18 patients each. The isolated Pseudomonas were sensitive to carbenicillin and E.Coli were sensitive to nalidixic acid and amikacin.

In a retrospective study by Jagralmudi et al[70] of 91 consecutive acute leukemia patients treated between January 1997 and July 1999 at AIIMS, Delhi, 240 febrile episodes were recorded. Median age was 36 years. 78 episodes were without neutropenia and 162 episodes were associated with ANC<500/mm3 .In 48% of febrile neutropenia episodes infective foci could not be identified and infectious foci was documented in 52%. In febrile neutropenia, the most common site of infection was chest (35. 7%), followed by skin and soft tissue (13%), GIT (7%) and genitourinary tract (6%). Gram positive organisms were isolated in 52.8% and gram negative organisms in 42.8% of isolates. 2 patients had candidiasis and 1 patient had aspergillus infection.2 patients had pulmonary tuberculosis infection. 79% of episodes received third generation cephalosporin and aminoglycoside combination. In 52.5% of febrile episodes second line antibiotics and antifungals were used. 11 of 91 patients died of complications related to infection.

In a prospective study by Mathur et al[71] of over 2 years among 96 patients with hematological malignancies, 119 episodes of febrile neutropenia were documented. Bacteremia was present in 35 episodes. Gram-negative aerobes constituted 46% and gram positive organisms were isolated in 44%. Higher mortality was seen with Gram-negative bacteremia when compared to gram positive bacteremia. Enterococcus species, Staphylococcus aureus and E.coli were the predominant isolates. Anaerobes contributed to 4.4% of all isolates. Anaerobic bacteremia were polymicrobial and outcome was fatal.[71] Incidence of antimicrobial resistance was high among anaerobic as well as aerobic bacteria. A shift from predominating gram negative to a gram positive etiology was observed and reported in this study.

In a large retrospective analysis of 222 febrile neutropenic episodes (ANC < 500/mm^3) in acute lymphoblastic leukemia patients by Bakshi et al[72], 56% had no identifiable focus and 44% had documented focus of infection. The most common site of infection was lungs (27.3%). Gram negative bacteria was the predominant isolate (67%) whereas gram positive bacteria was isolated in 33%. Blood was the commonest site of isolation for gram negative bacteria (5o%) followed by urine (32.6%). The most common gram-negative isolate was Escherichia coli (45.7%). The commonest site of isolation for gram positive bacteria was Blood (78.3%). The predominant gram-positive bacterial isolate was Staphylococcus aureus (39%). 22 fungal isolates were

documented, the majority of which were isolated from urine. 19 out of the 22 fungal isolates were detected in induction phase of chemotherapy. 42.8% of febrile neutropenic episodes improved with first-line antibiotic therapy and 57.2% of episodes required modification of first line antibiotic therapy. 38.7% of febrile neutropenic episodes required antifungal therapy. Among the 13 deaths, 6 deaths happened during induction and 6 during consolidation / intensification phase. The commonest cause of death was pneumonia and 7 had fungal infection. The majority of fungal infections were detected during induction chemotherapy.

In a retrospective analysis by Gupta et al[73] of 382 febrile episodes in non-M3 acute myeloid leukemia patients who underwent protocol induction and consolidation chemotherapy at AIIMS,Delhi, the median age was 28 years ranging from 2 to 61 years .347 febrile episodes had neutropenia (induction phase 172, consolidation phase 175) and 35 episodes were non neutropenic (induction 16, consolidation 19). Only in 64% of the febrile episodes infectious foci could be identified by either microbiological, radiological or on clinical grounds. The most common site of infection, both during induction and consolidation phase was lung. Gram-negative organisms were the predominant isolates. The number of febrile episodes with possible / probable definite fungal infection was 60 episodes. Six cases of tuberculosis and 3 cases of malaria were also identified. Out of the nineteen deaths, 17 occurred during

induction and 2 during consolidation. 12 out of 17 infection related deaths were possibly due to fungal infections.

Retrospective analysis of 432 patients from Tata Memorial Hospital, Mumbai with acute lymphoblastic leukemia over a 5 year time period generated data regarding 499 consequtive febrile episodes. Various antibiotic combinations used empirically were compared. 92% of febrile episodes qualified for febrile neutropenia. Lung was the most common site of clinical focus for infection. Pseudomonas aeruginosa (27.27%) was the commonest pathogen isolated. Response rate to first-line empirical antibiotic combination was 61.92%, with ceftazidime and amikacin combination producing the best response rate of 65.69%.[74] Uniform antibiotic policy resulted in a significant decrease in mortality. 11 patients had documented fungal infection out of which 8 patients had favorable outcome.

In a retrospective analysis of blood stream infections among all inpatients of Medical Oncology department at TMH Mumbai by Prabash et al[75] during the year 2007 revealed 484 isolates. Gram negative isolates were the predominant constituting 68.18% and gram positive isolates constituted 31.81%. Of the 484 isolates 69.42% were from peripheral blood, 20.87% from peripherally inserted central catheter (PICC), 7.23% from catheter tip culture and 2.27% from central catheter. The most common isolate was Pseudomonas

(30.37%), followed by Staph aureus (12.6%), Acinetobacter (11.57%), E.coli (10.95%).Among the gram positive isolates Staph aureus was the commonest isolate (72.73%). Among the extended spectrum beta lactamase (ESBL) producing isolates, E.coli constituted 50.94%. Peripheral blood was the commonest source for ESBL isolates (86%). Only 27.1% of gram negative isolates were sensitive to ceftriaxone. Gram negative isolates were 48.8% sensitive to piperacillin-tazobactam combination and 58.5% sensitive to cefoperazone-sulbactam combination. Sensitivity of gram negative isolates to meropenem is 71.1% and Klebsiella pneumonia did not exhibit resistance to meropenem. 4.5% of Streptococcal isolates were resistant to both vancomycin and teicoplanin. Resistance of Enterococcus to vancomycin was 50% and teicoplanin 15%. There was no resistance to linezolid.

In a report of 304 allogeneic HSCT done at Christian Medical College,Vellore, febrile neutropenia occured in all transplants. 415 infections were documented which included viral (42.9%), bacterial (34.9%), fungal (15.9%) and other infections (6.3%) including tuberculosis. Gram-negative bacteria were the predominant bacterial pathogens (80%) as compared to gram-positive (20%) bacteria. Nonfermenting Gram-negative bacteria (NFGNB) were the commonest gram negative isolate (24.9%) followed by Pseudomonas (17.9%), Escherichia coli (17.9%) and Klebsiella (9.7%). Blood was the commonest source of positive cultures (53.7%) followed by urine

(25.5%) and sputum (8.9%). Viral infections were documented in 43.7% of transplants. Herpes group of viruses, Cytomegalovirus and transfusion-related hepatitis were the commonly documented viral infections. 19.7% transplants had 66 documented fungal infections. Aspergillus species (69.7%) was the commonest fungal infection followed by Candida (22.2%) and Zygomycetes (8.1%). Tubercular infection was seen in 2.3% of the transplants. 7.8% of the transplants had suspected or documented catheter infection.[76]

The above described Indian data on high risk febrile neutropenia show that gram negative bacteria are still the predominant organism (Table 4). Use of first line antibiotics was non uniform in some of the reports. Many reports combined FN and non neutropenic fever. Impact of G-CSF usage has not been reported. Catheter related infections has not been described. With this above background we conducted this study with defined parameters and uniform antimicrobial policy.

Table 4. Recent Indian data on febrile neutropenia

Study (ref no)	Centre	No of FN	Year	positive culture %	Gram positive %	Gram negative %
67	CIA(WIA)	313	2004-06	37.3	22.6	37.1
70	AIIMS	162	1997-99	35	52.8	42.8
71	AIIMS	119	2002	30	44	46
72	AIIMS	222	2008	44	33	67
73	AIIMS	347	2001-06	21	40	60

MATERIALS AND METHODS

Study design and center

Prospective, observational, single institutional study conducted under medical oncology department including pediatric ward at Adyar Cancer Institute, Chennai.

Study duration

The study was conducted from January 2011 to December 2011

Defenitions:

1. Neutropenia-

Defined as a neutrophil count < 500 cells/mm^3 or a neutrophil count of < 1000 cells/mm^3 which is predicted to decrease to < 500 cells/mm^3 within the next 48-72hrs.

2. Fever-

Defined as a single oral temperature of $\geq 101^0$F or an oral temperature of 100.4^0F lasting one hour or more in the absence of obvious environmental causes.

3. FN episode-

Presence of both fever and neutropenia in a patient. The entire course of FN in a patient during or following a single cycle of chemotherapy was considered as one episode.

4. Types of FN-

- Microbiologically documented infection
- Clinically documented infection without microbiological evidence (presence of physical or radiological finding compatible with underlying infection)
- Fever of unknown origin (FUO) i.e without clinically suspected site or microbiological evidence.

5. High risk FN-

- Inpatient status at time of development of fever
- Significant medical comorbidity or clinically unstable
- Anticipated ANC< 100 for > 7 days
- Hepatic or renal insufficiency
- Pneumonia or other complex infection
- Grade 3 or 4 mucositis

6. Profound neutropenia-

ANC < 100 cells/mm^3

7. Bacterial infection-

Bacterial infection were documented on positive cultures from any sites like catheter, peripheral blood, sputum, urine and pus.

8. Fungal infections-

Documented as probable, possible and proven fungal infection based on EORTC/MSG criteria (described in review of literature).

9. Catheter related infection-

Central venous catheter and peripheral blood culture are done with automated bacTalert method. Patient was considered to have catheter related infection if same organism with same susceptibility pattern are grown on catheter tip and peripheral blood culture or if culture from catheter and peripheral blood has same organism and culture from catheter becomes positive 2 hours before peripheral blood culture.

Inclusion criteria:

Inpatients of all age groups with high risk FN during intensive therapy of acute leukemia

- AML during all phases of treatment (induction and consolidation)
- ALL during induction, consolidation and reinduction.

Exclusion criteria:

- Low risk febrile neutropenia
- Patients who are already on IV antibiotics for greater than 24 hours prior to development of FN
- Patients with high risk FN with underlying diagnosis other than acute leukemia

Evaluation:

A detailed history and a meticulous physical examination were done keeping in mind that typical symptoms and signs of infection may not be present. Special attention was given to common source of infective foci like lungs, vascular catheter, throat, oral cavity, paranasal sinuses, perineum, skin and soft tissue, bone marrow procedure site. Fundus was carefully examined. The initial investigations included the following:

- Complete blood cell count and manual differential count.
- Serum biochemistry including liver function tests, renal function tests and electrolytes. Two sets of blood cultures (each set included an aerobic and an anaerobic culture) from two different sites. If central venous catheter was present, one set of culture was taken from catheter.
- Blood cultures from each lumen of the central venous catheter if one was present.
- Urine culture

- Chest radiograph

Cultures were obtained before instituting antibiotics, however febrile neutropenia was a medical emergency and problems with drawing cultures did not delay the start of antibiotics.

First line antibiotics:

- Piperacillin +Tazobactam 100mg/kg per dose IV 6- 8hrly and amikacin 15mg/kg iv od

Second line antibiotics:

- Imipenem 60 mg/kg/day i.v.,6 hrly
- Meropenem 60 mg/kg/day i.v, 8 hrly

Re evaluation:

It was an ongoing process. Patients were examined daily for any new focus of infection, new signs, bleeding manifestations, hemodynamic stability. After 1st line empiric therapy, overall response was evaluated in 3days. Febrile episode was considered responding if

- decreasing fever trend
- signs and symptoms of infection are stable or improving
- patient hemodynamically stable

For afebrile patients, initial antibiotic regime was continued till resolution of neutropenia or for 2 weeks whichever was earlier.

Febrile episode was considered non responding if

- persistently or intermittently febrile
- signs and symptoms of infection are not improving
- patient hemodynamically unstable
- persistent positive blood culture.

Antifungal therapy was initiated for FUO greater than 4 days of empiric antibiotic therapy as well as for patients with clinical/radiological suspicion of fungal infection and was continued for the duration of neutropenia.

Modifications of the initial antibiotic regime was made on the basis of culture and sensitivity data thereby narrowing down the spectrum and using more specific antibiotics. If no source of infection was documented, the initial empiric antibacterial regime was not changed solely on the basis of persistent fever in a clinically stable patient. Two sets of blood cultures from different sites was obtained during each temperature spike in patients with persistent neutropenic fever with an interval of at least 24 hours between cultures.

Indications for teicoplanin:

- Clinically apparent, serious catheter related infection
- Blood culture positive for gram positive bacterium prior to final identification and susceptibility testing
- Known colonization with penicillin/cephalosporin resistant Pneumococci/MRSA
- Hypotension without an identified pathogen
- Soft tissue infection
- Pneumonia not responding to gram negative antibiotics
- Severe mucositis

Antibiotic prophylaxis:

As per existing departmental policy, antibacterial prophylaxis was not routinely used.

Antifungal prophylaxis:

All patients of acute myeloid leukemia received fluconazole prophylaxis during all protocol chemotherapy cycles. No antifungal prophylaxis was used in patients of ALL.

Antiviral prophylaxis:

No routine acyclovir prophylaxis was used

Therapeutic antifungals:

Conventional amphotericin B was used as the predominant first line antifungal at a dose of 1 mg/kg/day intra venous. However voriconazole was also used as first line antifungal based on physicians discretion in suspected invasive aspergillosis and in cases with difficult I.V access.

Second line antifungals were used in case of unresponsiveness/toxicity to first line therapy.

Central venous access management:

Central venous access devices are inserted under strict aseptic precautions in minor theatre and occasionally at bed side if the patient was sick. Chlorhexidine wash was given prior to insertion. Weekly twice chlorhexidine dressing of CVC was done under strict aseptic precautions at minor theatre. Transparent patch was used for dressing of central venous catheters to monitor exit site infection. Separate bed side 100 ml heparinised saline for individualized use of all patients with central venous catheters on a daily basis was enforced. Catheter manipulation at ward was done under strict aseptic techniques.

End points of study:

1. Recovery from febrile neutropenia and resolution of infective foci
2. Death

Data analysis and statistical methods:

- Outcomes of FN was correlated with clinical and microbiological parameters
- Success rate of various antibiotics was assessed
- Descriptive statistics was used for clinical and microbiological profile of FN.
- Chisquare analysis and student's t test was used to look for association with febrile neutropenia outcomes and various parameters studied
- P value < .o5 was considered statistically significant
- All statistic analysis was done by SPSS version 13.0

RESULTS

Baseline characteristics:

During the study period, 115 febrile episodes in 66 acute leukemia patients qualified for the inclusion criteria. The baseline diagnosis and treatment setting including number of FN episodes in each phase of protocol chemotherapy are summarized in Table 5. Acute myeloid leukemia (AML) in induction phase was the most common treatment setting followed by consolidation phase of AML. The Acute lymphoblastic leukemia (ALL) induction constituted 11.2% of febrile episodes followed by the other phases of treatment.

Table 5.Baseline diagnosis and frequency of enrolled FN episodes (n=115)

Treatment setting	Number of FN episodes	Percentage
AML induction	50	43.5
AML consolidation	43	37.4
ALL induction	13	11.3
ALL reinduction	5	4.4
ALL consolidation	4	3.4

Age group of patients ranged from 2 years to 75 years. The median age was 19 years. The 2 year old child had ALL and received high risk arm of BFM 95 protocol. The 75 year old gentleman had AML and received standard

protocol chemotherapy. Number of patients above 60 years were 5, out of whom 4 of them had AML. 70.4% of the episodes occurred in male and the rest 29.6% in females. In 54.7% of the FN episodes, disease was not in remission. 28.7% of FN required Intensive care unit admission and specialized care.

Maximum frequency of febrile episode onset happened on day 2 and day 3 of neutropenia, each contributing to 23.5% individually. 73% of febrile episodes started within first 4 days of neutropenia followed by gradual decline in the frequency of febrile episodes and 95.5% of febrile episodes started within first 10 days of neutropenia (Figure 1). The median duration of neutropenia at fever onset is 3 days.

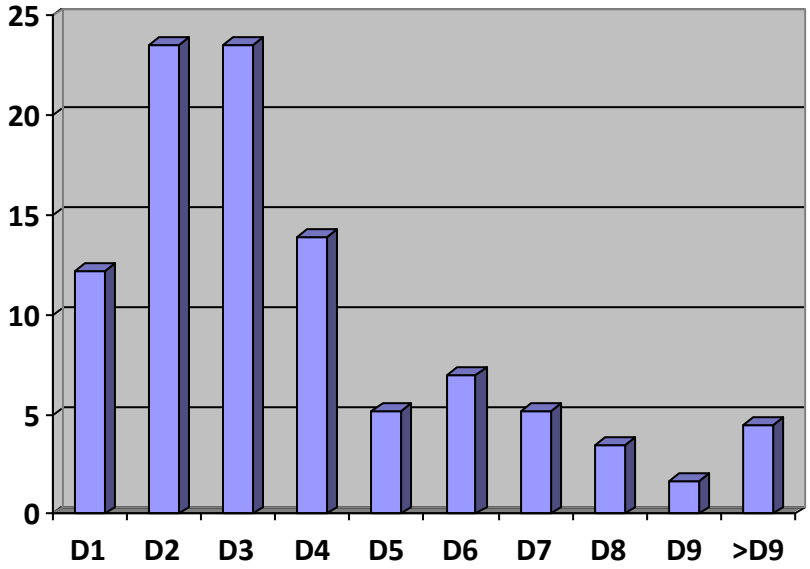

Figure 1. Frequency of fever onset during neutropenia

The day of prior chemotherapy cycle at onset of febrile neutropenia, ANC at fever onset, nadir ANC and duration of fever was documented for all FN episodes. The median day of chemotherapy cycle at onset of fever was day 10. The median of nadir ANC was 30cells/mm^3 and 87.8% of the febrile episodes had ANC < 100cells/mm^3 indicating that majority of FN had profound neutropenia. The median ANC at onset of FN was 80cells/mm^3 and the average number of days for which fever lasted during FN episode was 7 (Table 6).

Table 6. Febrile neutropenia charecteristics

Characteristics	Median
Day of cycle at fever onset	10
Nadir ANC	30 cells/mm^3
ANC at fever onset	80 cells/mm^3
Number of days of fever	7

Types of central venous catheter:

Out of 115 FN episodes, 94 (81.7%) had indwelling central venous catheter at the time of diagnosis of FN. Peripherally inserted central catheter (PICC) was present in 60 FN episodes, followed by subclavian vein catheter in 31 episodes, Hickman catheter in 2 episodes and PORT in 1 episode.

Profile of infections:

All potential site of infective foci during FN was meticulously examined and documented. Infective foci was identified clinically in 81 episodes (70.4%). All relevant radiological data, wherever applicable were incorporated into assignment of clinical foci. Lung was the clinical foci in 29 episodes (25.2%) followed by vascular catheter in 20 episodes (17.4%), skin and soft tissue in 11 episodes (9.6%), gastro intestinal (GI) tract in 10 episodes (8.7%), perineum in 7 episodes (6.1%), urinary tract in 2 episodes (1.7%), oral cavity and sinus in 1 episode (.9%) each (Figure.2)

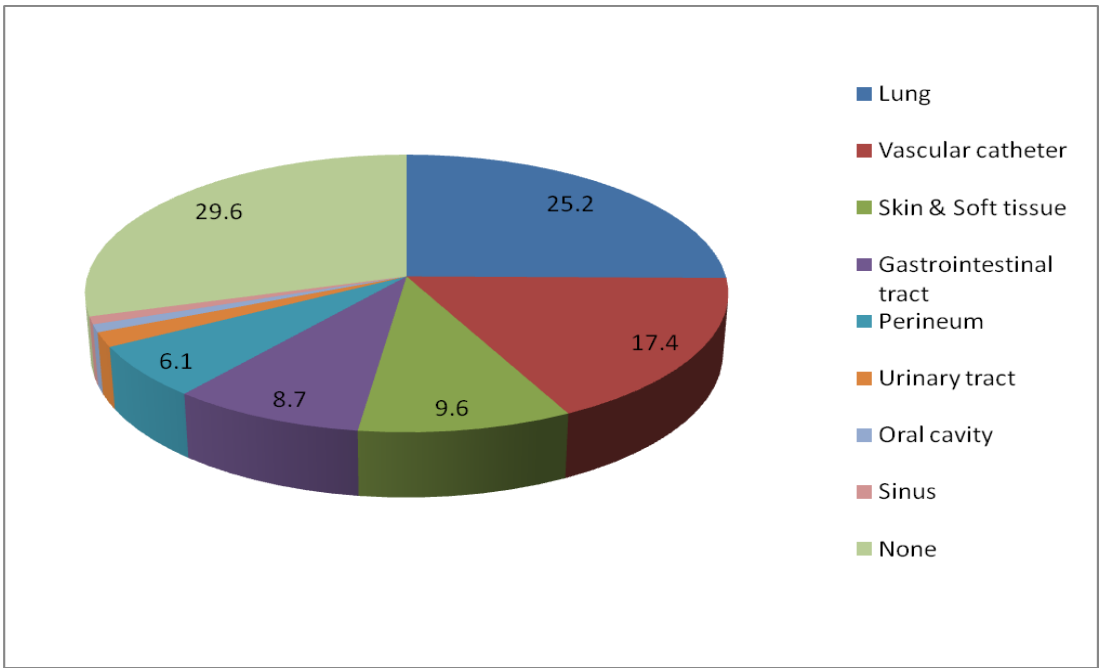

Figure 2. Clinical foci of infection (n=115)

Microbiological documentation was possible in 38 FN episodes with a total of 40 isolates. The catheter blood culture contributed to majority of culture with 19 isolates followed by stool culture with 7 isolates, sputum culture with 6 isolates, 4 isolates from pus culture, 2 isolates from urine culture and 2 isolates from perianal wound swab culture (Table 7). In 34 episodes (29.6%) infective foci could not be identified clinically as well as microbiologically and was classified as FUO.

Table 7: Source of microbiological isolates (n=40)

Source	Number	Percentage
Catheter blood	19	47.5
Stool	7	17.5
Sputum	6	15
Pus	4	10
Urine	2	5
Perianal wound swab	2	5

Spectrum of microbiological isolates:

A total of 40 isolates were identified. Among the 36 bacterial isolates, gram negative organisms constituted 21 isolates (58.3%) and gram positive organisms constituted 15 isolates (41.7%). Pseudomonas was isolated in 11 episodes, followed by Staphylococcus aureus in 10 episodes, Klebsiella

pneumonia in 5 episodes, Enterococcus species in 3 episodes, E.coli in 3 episodes, Streptococcus pneumonia and Acinetobacter species in 2 episodes each. Candida species and Aspergillus was isolated in 2 episodes each (Table 8). Among the catheter blood culture isolates 10 was Pseudomonas followed by 5 Staphylococcus isolates, 2 Candida species, 1 Acinetobacter species and 1 Klebsiella pneumonia species.

Table 8. Spectrum of microbiological isolates (n=40)

Organism	Frequency	Percentage
Pseudomonas	11	27.5
Staphylococcus aureus	10	25
Klebsiella pneumonia	5	12.5
E.coli	3	7.5
Enterococcus species	3	7.5
Streptococcus pneumonia	2	5
Acinetobacter species	2	5
Candida species	2	5
Aspergillus	2	5

Antibiotic usage:

First line antibiotics

Piperacillin-tazobactam + amikacin was used as first line antibiotic in 107 episodes (93%). Single agent piperacillin-tazobactum was used as first line antibiotic in 7 episodes (6.1%). Meropenem was used as first line antibiotic in 1 episode (0.9%), as shown in Table 9.

Second line antibiotics

Escalation to second line antibiotics was not necessary in 31 FN episodes (27%), whereas in 84 episodes (73%), second line antibiotics were used. Imipenem was used in 48 episodes (57.1%), followed by teicoplanin in 19 episodes (22.6%), meropenem in15 episodes (17.9%) and linezolid in 2 episodes (2.4%), as shown in Table 10.

Table 9.First line antibiotic usage frequency

Antibiotic	Frequency of usage	Percentage
Piperacillin-tazobactum + amikacin	107	93
Piperacillin-tazobactum	7	6.1
Meropenem	1	0.9

Table 10.Second line antibiotics usage frequency

Antibiotic	Frequency of usage	Percentage
Imipenem	48	57.1
Teicoplanin	19	22.6
Meropenem	15	17.9
Linezolid	2	2.4

The median number of days for which first line antibiotics were continued without escalation was 4 days. The median number of days of second line antibiotic usage was 8 days.

Antibiotic sensitivity pattern:

Gram negative bacteria are sensitive to cefoperazone-sulbactum, piperacillin-tazobactum, carbapenem and amikacin. The sensitivity pattern of gram negative bacterial isolates are shown in Table 11. There were no extended spectrum beta lactamase (ESBL) isolates. Methicillin resistant Staph aureus (MRSA) was identified in 1 episode. All the Enterococcus isolates were resistant to beta lactam antibiotics as well as carbapenems. All gram positive isolates were 100% sensitive to glycopeptides and linezolid. Sensitivity pattern of Staph aureus is shown in Table 12

Table 11. Antibiotic sensitivity pattern among gram negative isolates (n=21)

Antibiotic	Sensitivity percentage
Ceftazidime	33.3
Cefoperazone + sulbactum	95.2
Piperacillin + tazobactum	95.2
Imipenem	100
Meropenem	100
Amikacin	95.2

Table 12. Antibiotic sensitivity pattern of Staph aureus (n=10)

Antibiotic	Sensitivity percentage
Vancomycin	100
Teicoplanin	100
Linezolid	100
Piperacillin+tazobactum	90
Cefoperazone+sulbactum	90
Carbapenem	90
Amikacin	90

Antifungal usage

First line antifungals

55 episodes of FN (47.8%), required antifungal treatment and the rest 60 episodes (52.2%), did not require antifungal treatment. Empirical antifungal therapy was started in 41 FN episodes. Out of 55 episodes requiring antifungal usage, amphotericin B was used in 31 episodes (56.4%) followed by voriconazole in 22 episodes, caspofungin and posaconazole in 1 episode each as shown in Table 13. Average number of days for which first line antifungals were used was 11 days.

Second line antifungals

16 episodes required change of first line antifungal therapy either due to inadequate response or toxicity concerns. Voriconazole was used in 11 of these episodes and caspofungin in 5 episodes.

Table 13.Frequency of first line antifungal usage

Antifungal agent	Frequency of usage in FN episodes	Percentage
Amphotericin B	31	56.4
Voriconazole	22	40
Caspofungin	1	1.8
Posaconazole	1	1.8

Invasive fungal disease:

As per EORTC/MSG guidelines, 18 episodes were assigned to some form of invasive fungal disease (IFD). Invasive candidemia (blood culture positivity) was documented in 2 FN episodes, one during ALL induction and another during AML consolidation. One case of AML induction was proven to have sino-nasal aspergillosis by histopathological demonstration of aspergillus hyphae from sino-nasal specimen biopsy.15 FN episodes had possible / probable IFD as shown in Table 14. Out of 15 FN episodes with possible / probable IFD, 8 of them were in AML induction, 5 in AML consolidation and 2 in ALL induction.

Table 14.Frequency of IFD

Category	Number	Percentage
Proven IFD[a]	3(2+1)	2.7
Possible/probable IFD[b]	15(14+1)	13
None	97	84.3

a. 2 FN episodes with blood culture positive for Candida species and 1with invasive aspergillosis

b. 14 FN based on radiological criteria and 1 with sputum culture positive for Aspergillosis

G-CSF usage:

G-CSF was used in 70 episodes of FN (60.9%). All AML consolidation patients with high risk FN received G-CSF invariably (43 episodes). 15 FN episodes in AML induction required G-CSF. 6 episodes of ALL induction, 3 episodes of ALL consolidation as well as 3 episodes of ALL reinduction required G-CSF usage as shown in Table15. The average number of days of G-CSF usage during AML consolidation was 11.5 days, AML induction 9.5 days, ALL induction 5.5 days, ALL consolidation 7.3 days and ALL reinduction 6.6 days.

Table 15.Frequency of G-CSF usage

Treatment setting	Frequency of G-CSF usage	Average number of days of G-CSF usage	Percentage
AML consolidation	43	11.5	61.4
AML induction	15	9.5	21.4
ALL induction	6	5.5	8.6
ALL consolidation	3	7.3	4.3
ALL reinduction	3	6.6	4.3

Outcome:

11 (9.6%) out of 115 high risk FN had fatal outcome while the rest 104 FN episodes (90.4%) had resolution of FN and were discharged or continued on further management

Potential factors influencing outcome:

Age

In 8 FN episodes with age greater than 6o, fatal outcome occurred in 1 episode (12.5%). The number of fatal outcomes in 107 FN episodes with age less than 60 was 10 (9.3%). The p value was 0.565, indicating that age did not influence FN outcome in this study.

Gender

In males, number of fatal outcomes in 81 FN episodes was 8 (9.9%). In females, number of fatal outcomes in 34 FN episodes was 3 (8.8%). The p value was 0.583 and indicates that gender did not influence the outcome of FN.

Remission status

In 52 FN episodes with bone marrow in remission, fatal outcome occurred in 4 episodes (7.7%) whereas in 63 FN episodes with bone marrow

not in remission, fatal outcome occurred in 7 episodes (11.1%). The p value was 0.533 and was statistically insignificant

Duration of neutropenia at fever onset

From the statistical analysis of this study, it was found that the number of days of neutropenia prior to fever onset does not affect the outcome significantly.

Day of chemotherapy cycle at fever onset

As per analysis, the outcome of FN episode was not altered by the day of chemotherapy cycle at which fever starts.

Nadir ANC

The nadir ANC of chemotherapy cycle does not influence the outcome of FN significantly

ANC at fever onset

Outcome of FN episode was not influenced by ANC at fever onset.

G-CSF usage

FN outcome was not influenced by G-CSF usage in this study.

Lung infection

Number of fatal outcomes in 29 FN episodes with clinically suspected lung infection was 7 (24.1%), whereas the number of fatal outcomes in 86 FN episodes without ling infection was 4 (4.7%). The p value was 0.02 and indicates that development of lung infection during FN definitely influences the outcome as shown in Table 16

Table 16. Potential factors influencing outcome of high risk FN

Parameter		**No. of FN**	**Fatal Outcome in percentage**	**p Value**
Age	<60	107	10 (9.3)	0.565
	>60	8	1 (12.5)	
Gender	Male	81	8 (9.9)	0.583
	Female	34	3 (8.8)	
Clinical focus of lung infection	Yes	29	7 (24.1)	**0.02**
	No	86	4 (4.7)	
Remission status	yes	52	4 (7.7)	0.533
	No	63	7 (11.1)	

DISCUSSION

Over the years, series of well conducted studies have generated necessary information to reduce the incidence, severity and mortality of febrile neutropenia. The early empiric use of antimicrobial therapy remains the corner stone of strategy for management of high risk FN. There are various guidelines to facilitate choice of antimicrobial therapy but the final choice depends on local isolates and sensitivity pattern. With this background a prospective study was planned to generate comprehensive data on high risk FN in acute leukemia patients so that our clinical practice could be updated.

Febrile neutropenia characteristics:

In our study the median duration of day of chemotherapy cycle at fever onset was 10 days and the median duration of neutropenia at fever onset was 3 days. Park et al[78] reported median time lag with the onset of fever and neutropenia as 4.3 days. Louw et al[77] reported that the median duration between delivery of chemotherapy and onset of FN episode was 14 days and that FN episode occurred at a median of 3 days from onset of neutropenia.

In our study the nadir ANC was 30 cells/mm3, whereas Louw et al[77] reported a nadir ANC of 10 cells/mm^3 in his study.

The average number of days for which fever lasted per FN episode in this study was 7 days, whereas the study by Park et al[78] reported that the median duration of fever per FN episode was 10 days. Thus the baseline characteristics of febrile neutropenia varies amongst the studies.

Clinical foci of infection:

Lung has consistently been the commonest site of infective foci in acute leukemia patients with FN. In this study lung was the most common site of identifiable infective foci (25.2%). Kumar et al[68] reported lung as the commonest site of infective foci (37.9%). Jagralmudi et al[70] reported that chest was clinical foci of infection in 35.7% of FN. Bakshi et al[72] reported chest as the infective foci in 27.3%. Gupta et al [73] also reported that lung was the most common site of infective foci.

Microbiological data:

Across the studies, frequency of microbiological documentation has been in range of 20-35%. In this study 33% of FN episode has documented microbiological data. However Kumar et al[68] had reported microbiological documentation in 58.2%. The predominant site of microbial isolate in this study was blood (47.5%). Bakshi et al[72] reported that the commonest site for microbial isolate was blood.

International studies[18-20] have reported that by the end of 20th century, 60%-70% of FN episodes was caused by gram positive bacteria. Recently various studies from developing countries have reported re emergence of gram negative bacteria in FN episode. In this study gram negative bacteria constituted 58.3% of bacterial isolates. Baskaran et al[24] as well as Santa et al[67] had reported that gram negative organisms were the predominant bacterial isolates. Bakshi et al[72] reported that gram negative bacterial isolates were predominant (67%). Prabash et al[75] reported that gram negative isolates constituted 68.18% of bacterial isolates. Gupta et al[73] reported that gram negative isolates were the predominant bacterial isolates The most common gram negative bacteria isolated in this study was Pseudomonas. Raje et al[74] reported that Pseudomonas was the commonest microbial pathogen isolated. Similarly Prabash et al[75] reported that the commonest isolate was pseudomonas.

The commonest gram positive isolate in our study was Staph aureus. Prabash et al[75] reported that Staph aureus constituted 72.3% of gram positive isolates in his study. Pseudomonas was the commonest isolate from CVC blood culture in this study. Sherertz et al[27] had reported that coagulase negative Staphylococcus aureus was the commonest isolate from CVC blood culture in his study and that Pseudomonas was frequently detected as well. The pattern of bacterial isolates in our study is similar to that from other oncological centers in India.

Antibiotic spectrum:

The gram negative isolates in our study were sensitive to ceftazidime in only 33.3% but were 100% sensitive to carbapenem 95.2% sensitive to amikacin, cefoperzone-sulbactum and piperacillin-tazobactum. Ghosh et al[79] had reported that gram negative isolates were only 15.9% sensitive to ceftazidime. Prabash et al[75] had reported that gram negative isolates were 58.5% sensitive to cefoperazone-sulbactum and 48.8% sensitive to piperacillin-tazobactum. Ghosh et al[79] had reported that gram negative isolates were 84.1% sensitive to cefoperazone-sulbactum, 65.9% sensitive to piperacillin-tazobactum, 63.7% sensitive to imipenem and 48.8% sensitive to amikacin.

An interesting finding of our study is that the prevelance of MRSA among Staph aureus was 10%, whereas Ghosh et al [79] had reported MRSA prevelance of 20% among Staph aureus isolates. There was no resistance to vancomycin and teicoplanin among gram positive isolates including Enterococcus species in our study. Ghosh et al[79] had reported that the prevelance of vancomycin resistant Enteroccus (VRE) was 25% in his study.

The exact reason why the in vitro sensitivity of microbial isolates to various antibiotics is highly variable across centers is not clear. The likely reason is that epidemiology of microbial organisms are dynamic and can vary between centers depending on local antibiotic policy, prudent use of antimicrobial therapy.

Antibiotic policy:

As per departmental policy, piperacillin-tazobactum + amikacin was uniformly used as first line empiric antibiotic in high risk FN for the entire year 2011. Cefoperazone-sulbactum was given drug holiday so as to prevent development of resistance. Guidelines on choice of empiric therapy in FN is varied. NCCN[43] recommends monotherapy with carbapenem or aminoglycoside with antipseudomonal cephalosporin as first line empiric therapy for high risk FN. In a resource constraint setting, it may not be prudent to use carbapenem as first line antibiotic and moreover gram negative isolates were 100% sensitive to carbapenem in our centre and prudent usage of carbepenem is crucial for preventing carbapenem resistance. In our study carbapenem was used only in 54.7% of high risk FN and underscores the fact that routine first line usage of carbapenem in high risk FN may not be necessary and should be tailored to needs of individual patients.

Antifungal therapy:

Preemptive antifungal therapy is presently not the standard of practice[44] whereas the routine practice as per IDSA guidelines is to initiate on empiric antifungal therapy in high risk FN.In our study 47.8% of FN episodes required therapeutic antifungal agent. Ghosh et al[79] had reported that 41.5% of FN episode in his study required therapeutic antifungal agent. Gupta et al[73] had reported that 51% of FN episodes required therapeutic antifungal agent. The high rate of therapeutic dose antifungal agent usage is due to present guidelines of using empiric antifungal therapy in high risk FN.

Factors influencing mortality:

The mortality rate of 9.6% in our study is comparable to other published data[80]. Age, gender, remission status, nadir ANC, ANC at fever onset, G-CSF usage did not influence outcome in this study. Park et al[78] reported that sex, duration of neutropenia and ANC at fever onset failed to influence outcome in FN. Ghosh et al[79] reported that nadir TLC< 200/µl and abnormal chest radiograph were associated with a fatal outcome. In this study clinical focus of lung infection was significantly associated with fatal outcome.

CONCLUSION

- 115 high risk FN episodes in intensive phase treatment of acute leukemia qualified for this study and gram negative isolates were the most common isolates (58.3%).
- Pseudomonas was the predominant gram negative isolate and Staph aureus was the most common gram positive isolate.
- There were no ESBL or VRE isolates
- Lung was the most common site of clinical focus of infection.
- Success rate of first line empiric antifungal agent was 70%.
- Overall 11 episodes (9.6%) had fatal outcome.
- Clinical focus of lung infection was significantly associated with mortality.
- Gram negative isolates are highly sensitive to cefoperazone-sulbactum and piperacillin-tazobactum
- Based on this data, first line empiric antibiotic therapy of cefoperazone-sulbactum+amikacin or piperacillin-tazobactum+amikacin seems justified.
- In a cost restraint scenario, Carbapenem and glycopeptide agents needs to be judiciously used.

REFERENCES

1. Hughes WT. Fatal infections in childhood leukemia. Am J Dis Child 1971; 122:283-7.
2. Levine AS, Schimpff SC, Graw RG, Jr. et al. Hematologic malignancies and other marrow failure states: progress in the management of complicating infections. Semin Hematol 1974; 11:141-202.
3. Pizzo PA. Evaluation of fever in the patient with cancer. Eur J Cancer Clin Oncol 1989; 25 Suppl 2:S9-16.
4. Feld R, Bodey GP. Infections in patients with malignant lymphoma treated with combination chemotherapy. Cancer 1977; 39:1018-25.
5. Hersh EM, Bodey GP, Nies BA, et al. Causes of Death in Acute Leukemia: A Ten Year Study of 414 Patients from 1954-1963. JAMA 1965; 193:105-9.
6. Bodey GP, Buckley M, Sathe YS, et al. Quantitative relationships between circulating leukocytes and infections in patients with acute leukemia. Ann Intern Med 1996; 64:328-48.

7. Longo DL, Duffey PL, DeVita VT, Jr., et al. The calculation of actual or received dose intensity: a comparison of published methods. J Clin Oncol 1991; 9:2042-51.
8. Farber S, Diamond LK. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. N Engl J Med 1948;238(23):787-93.
9. Bodey GP. The changing face of febrile neutropenia - from monotherapy to moulds to mucositis.Fever and neutropenia: the early years. J Antimicrob Chemother 2009;63 Suppl 1:3-13.
10. Rintala E. Incidence and clinical significance of positive blood cultures in febrile episodes of patients with hematological malignancies. Scand J Infect Dis 1994;26(1):77-84.
11. Madani TA. Clinical infections and bloodstream isolates associated with fever in patients undergoing chemotherapy for acute myeloid leukemia. Infection 2000;28(6):367-73.
12. Perola O, Nousiainen T, Pentikäinen J, Laatikainen A, Katila ML. Infections and bacterial colonization during cytotoxic therapy in patients with acute leukemia. Eur J Clin Microbiol Infect Dis 2005;24(11):766-8.
13. Gencer S, Salepci T, Ozer S. Evaluation of infectious etiology and prognostic risk factors of febrile episodes in neutropenic cancer patients. J Infect 2003;47(1):65-72.

14. Gafter-Gvili A, Paul M, Fraser A, Leibovici L. Antibiotic prophylaxis in neutropenic patients. Isr Med Assoc J 2007;9(6):460-2.
15. De Pauw BE, Verweij PE. Infections in patients with hematologic malignancies. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005.
16. Sickles EA, Greene WH, Wiernik PH. Clinical presentation of infection in granulocytopenic patients.Arch Intern Med 1975;135(5):715-9.
17. Klastersky J. Empiric treatment of infections in neutropenic patients with cancer. Rev Infect Dis 1983;5 Suppl 1:S21-31.
18. Cometta A, Zinner S, De Bock R, et al. Piperacillin-tazobactum plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. Antimicrob Agents Chemother 1995; 39: 445-52.
19. Cometta A, Calandra T, Gaya H, et al. Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. Antimicrob Agents Chemother 1996;40: 1108-15.
20. Gonalez-Barca E, Fernandez-Sevilla A, Carratala J, et al. Prospective study of 288 episodes of bacteremia in neutropenic patients in a single institution. Eur J Clin Microbiol Infect Dis 1996; 15: 291-6.

21. Cappellano P, Viscoli C, Bruzzi P,et al.Epidemiology and risk factors for blood stream infections after allogenic hematopoietic stem cell trans. New Microbiol 2007; 30:89-99.
22. Lowder JN, Lazarus HM, Herzig RH, et al. Bacteremias and fungemias in oncological patients with central venous catheters. Arch Intern Med 1982;142:1456-9.
23. Viscoli C, Bruzzi P, Castagnola E, et al. Factors associated with bacteremia in febrile, granulocytopenic cancer patients. Eur J Cancer 1994;30A:430-7.
24. Baskaran ND, Gan GG, Adeeba K, et al. Bacteremia in patients with febrile neutropenia after chemotherapy at a university medical center in Malaysia. Int J Infect Dis 2007; 6: 513-17.
25. Hughes WT, Amstrong D, Bodey GP, et al, 2002. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002; 34: 730-51.
26. Heard SO, Wagle M, Vajayakumar E, McLean S, Brueggemann A, Napolitano LM et al (1998) Influence of triple-lumen central venous catheters coated with chlorhexidine and silver sulfadiazine on the incidence of catheter-related bacteremia. Arch Intern Med 158:81–87.
27. Sherertz RJ, Raad II, Belani A, Koo LC, Rand KH, Pickett DL et al (1990) Three year experience with sonicated vascular catheter cultures in a clinical microbiology laboratory. J Clin Microbiol 28:76–82.

28. Seifert H, Cornely O, Seggewiss K, Deceker M, Stefanik D,Wisplinghoff H et al (2003) Bloodstream infection in neutropenic cancer patients related to short-term nontunnelled catheters determined by quantitative blood cultrures, differential time to positivity, and molecular epidemiological typing with pulsedfield gel electrophoresis. J Clin Microbiol 41:118–123.
29. Goetz AM, Wagener MM, Miller JM, Muder RR (1998) Risk of infection due to central venous catheters: effect of site of placement and catheter type. Infect Control Hosp Epidemiol 19:842–845.
30. Merrer J, De Jonghe B, Golliot F, Lefrant JY, Raffy B, Barre E et al (2001) Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. JAMA 286:700–707.
31. Mimoz O, Pieroni L, Lawrence C, Edouard A, Costa Y, Samii K et al (1996) Prospective, randomized trial of two antiseptic solutions for prevention of central venous or arterial catheter colonization and infection in intensive care unit patients. Crit Care Med 24:1818–1823.
32. Maki DG, Ringer M, Alvarado CJ (1991) Prospective randomized trial of povidone–iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. Lancet 338:339–343.

33. Little JR, Maurray PR, Traynor PS, Spitznagel E (1999) A randomized trial of povidone–iodine compared with iodine tincture for venipuncture site disinfection: effects on rates of blood culture contamination. Am J Med 107:119–125.
34. Ljungman P, Hagglund H, Bjorkstrand B, Lonnqvist B, Ringden O (1997) Preoperative teicoplanin for prevention of gram-positive infections in neutropenic patients with indwelling central venous catheters: a randomized, controlled study. Support Care Cancer 5:485–488.
35. Van de Wetering M et al (2005) Prophylactic antibiotics for preventing early Gram-positive central venous catheter infections in oncology patients, a Cochrane systematic review. Cancer Treat Rev 31:186–196
36. Zakrzewska-Bode A, Muytjens HL, Liem KD, Hoogkamp-Korstanje JA (1995) Mupirocin resistance in coagulase-negative staphylococci, after topical prophylaxis for the reduction of colonization of central venous catheters. J Hosp Infect 31:189–193.
37. Bijma R, Girbes AR, Kleijer DJ, Zwaveling JH (1999) Preventing central venous catheter-related infection in a surgical intensive-care unit. Infect Control Hosp Epidemiol 20:618–620.
38. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease Catheter Related Blood Stream Infections in the ICU. N Eng J Med 2006; 355: 2725-32.

39. Talcott JA, Finberg R, Mayer RT, et al. the medical course of cancer patients with fever and neutropenia. Clinical identification of a low risk subgroup at presentation. Arch Intern Med 1988;148:2461-8.
40. Klastersky J, Paesmans M, Rubinstein EB, et al. The Multinational Association for Supportive Care Cancer risk index. A multinational scoring system for identifying low risk febrile neutropenic cancer patients. J Clin Oncol 2000;18:3038-51.
41. Chang HY, Rodrigues V, Narboni G, et al. Causes of death in adults with acute leukemia. Medicine 1976;55:259-68.
42. Schimpff S, Satterlee W, Young VM, et al. Empiric therapy with carbenicillin and gentamycin for febrile patients with cancer and granulocytopenia. N Engl J Med 1971;284:1061-5.
43. National Comprehensive Cancer Network. NCCN clinical practice guidelines in Oncology: prevention and treatment of cancer related infections (v2.2011).
44. Alison G. Freifeld, Eric J. Bow, Kent A, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases 2011;52(4):e56–93
45. DeGregorio MW, Lee WM, Linker CA, et al. Fungal infections in patients with acute leukemia. Am J Med 1982; 73:543–8.

46. Blijlevens NM, Donnelly JP, de Pauw BE. Impaired gut function as risk factor for invasive candidiasis in neutropenic patients.Br J Haematol 2002; 117:259–64.
47. Nucci M, Anaissie E. Revisiting the source of candidemia: skin or gut? Clin Infect Dis 2001; 33:1959–67.
48. Walsh TJ, Pappas P, Winston DJ, Lazarus HM, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002;346:225-34.
49. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408-15.
50. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin vs liposomal amphotericin B for empiric antifungal therapy in patients with persistent fever and neutropenia. N Eng J Med 2004; 351: 1391-1402.
51. Caillot D, Couaillier JF, Bernard A, et al. Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. J Clin Oncol 2001; 19:253–9.
52. Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis 2007; 44:373–9.

53. Kuhlman JE, Fishman EK, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, the role of CT in early diagnosis. Radiology 1985; 157:611–4.
54. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol 1997;15:139–47.
55. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis 2005; 41:1242-50.
56. De pauw B, Walsh TJ, Donnelly JP, et al; Revised definitions of invasive fungal disease from the European Organisation for Research and Treatment of Cancer and Infectious Disease Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008; 46: 1813-21.
57. Denning DW, Ribaud P,Milpied N et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 2002; 34:563–71.
58. Martens J, Raad I, Petrikkos G, et al. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory or intolerant of conventional antifungal therapy. Caspofungin Salvage Aspergillosis Study Group. Clin Infect Dis 2004; 34:1563–71.

59. Gafter-Gvili A, Fraser A, Paul M, et al. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 2005; 142:979–95.
60. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 2005; 353:977–87.
61. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009;15:1143–238.
62. Rotstein C, Bow EJ, Laverdiere M, et al. The Canadian Fluconazole Prophylaxis Study Group. Randomised placebo controlled trial of fluconazole prophylaxis for neutropenic cancer patients : benefit based on purpose and intensity of cytotoxic therapy. Clin Infect Dis. 1999;28:331-340.
63. Wingard JR, Carter SL, Walsh TJ, et al. The Blood and Marrow Transplant Clinical Trials Network. Results of a randomized, double blind trial of fluconazole(FLU) vs voriconazole(VORI) for the prevention of invasive fungal infections(IFI) in 600 allogenic blood and marrow transplant(BMT) patients. Blood 2007; 110: abstract 63.

64. Cornely OA. Maertens J, Winston DJ, et al. Posaconazole vs fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356:348-59.
65. Smith TJ, Khatcheressian J, Lyman GH. 2006 update of recommendations for the use of white blood cell growth factors: an evidence based clinical practice guidelines. J Clin Oncol.2006; 24:3187-205.
66. Hueser M, Ganser A, Bokemeyer C: American society of Clinical Oncology; National Comprehensive Cancer Network; European Organisation for Research and Treatment of Cancer. Use of colony-stimulating factors for chemotherapy-associated neutropenia: review of current guidelines. Semin Hematol.2007;44:148-56.
67. Santa A. Thesis on " Infectious complications in Children and Young Adults with Acute lymphoblastic leukemia in Southern India" submitted to The T N Dr.MGR Medical University in February 2007.
68. Kumar L, Kochupillai V, Bhujwala RA.Infections in acute myeloid leukemia. Study of 184 febrile episodes.J Assoc Physicians India1992;40(1):18-20.
69. Choudry VP, Tokuhochishi L, Gupta U, et al. Etiology of febrile episodes in children with acute lymphocytic leukemia. Indian J Med Res 1992; 96: 12-5.

70. Jagralmudi R,Kumar L, Kochupillai V, et al. Infections in acute leukemia: an analysis of 240 febrile episodes. Med Oncol 2000; 17(2): 111-16.
71. Mathur P, Chaudary R, Kumar et al. A study of bacteremia in febrile neutropenic patients at a tertiary care hospital with special reference to anerobes; Med Oncol 2002;19: 267-72.
72. Bakshi S, Padmanjali KS, Arya LS. Infections in childhood acute lymphoblastic leukemia: an analysis of 222 febrile neutropenic episodes. Pediatr Hematol Oncol 2008;25:385-92.
73. Gupta A, Singh M, Singh H, et al. Infections in acute myeloid leukemia: an analysis of 382 febrile episodes . Med Oncol 2009; 27 (4):1037-45.
74. Raje NS, Rao SR, Iyer RS, et al. Infection analysis in acute lymphoblastic leukemia: a report of 499 consecutive episodes in India. Pediatr Hematol Oncol. 1994;11:271-280.
75. Prabash K, Medhekar A, Ghadyapatil N et al. Blood stream infections in cancer patients: a single center experience of isolates and sensitivity pattern. Indian J Cancer.2010;47:184-8.
76. George B, Mathews V, Srivatsava A, et al. Infections among allogenic bone marrow transplant recipients in India. Bone Marrow Transplant. 2004;33:311-5.

77. Louw VJ, Westhuizen J, Rautenbach W et al. The antibiotic susceptibility of bacteria isolated from blood cultures during episodes of neutropenic fever in patients with acute myeloid leukaemia. South Afr J Epidemiol Infect 2010;25(2):09-11.
78. Park Y, Kim D, Park S et al. The suggestion of a risk stratification system for febrile neutropenia in patients with hematologic disease. Leukemia Research 34(2010) 294-300.
79. Ghosh I, Raina V, Kumar L et al. Profile of infections and outcome in high-risk febrile neutropenia: experience from a tertiary care cancer center in India.Med Oncol 2011. E pub(ahead of publication).
80. Kuderer NM, Dale DC, Crawford J, et al. Mortality, morbidity and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006; 106:2258-66.

PROFORMA

Name: **Age:** **Sex:** **OP no:**

Admission : 1) Ward 2) ICU 3) BMT

Diagnosis : 1) ALL 2) AML 3) NHL

4) HL 5) CML 6) Others

Disease Status : 1) Remission 2) Not in Remission

Treatment Setting : 1) ALL -Ind 2) ALL Cons 3) ALL RI

4) ALL Maint 5) AML Ind 6) AML Cons

7) Auto BMT 8) Allo BMT 9) Others

Duration of Neutropenia at the time of diagnosis of fever (days):

Day of cycle at onset of febrile Neutropenia : **Nadir TLC:**

ANC at fever onset : **Duration of fever (days):**

Number of previous febrile neutropenia episodes :

Presence of vascular catheter : **1)Yes** **2) No**

II) INFECTIVE FOCI :

1) Oral cavity 2) Lung 3) Gastrointestinal tract

4) Perineum 5) Urinary tract 6) Skin and soft tissue

7) Vascular catheter 8) Others (specify) 9) None

III) PRETREATMENT BLOOD TEST :

Haemoglobin WBC count

Platelet count

IV) PROPHYLACTIC MEDICATIONS:

V) MICROBIOLOGY:

SITE	ORGANISM	COLONY COUNT	SENSITIVITY	RESISTANCE
1.				
2.				
3.				
4.				

VI) VASCULAR CATHETER RELATED OBSERVATIONS:

Type of Catheter:

1) PICC (Single Lumen) 2) Subclavian catheter (Single Lumen)

3) Hickman Catheter (Double Lumen) 4) PORT

Catheter blood culture : 1) Positive Organism (Specify):

2) Negative

Peripheral blood culture: 1) Positive Organism (Specify):

2)Negative

Repeat Catheter blood culture : 1) Positive Organism (Specify):

2) Negative

Repeat Peripheral blood culture : 1) Positive Organism (Specify):

2) Negative

Catheter Tip Culture (If Positive): Organism (specify):

VII) ANTIBIOTICS:

	Drug	**Indication**	**Duration**	**Response**
First line				
Second line				

VIII ANTIFUNGALS :

Drug	**Indication**	**Duration**	**Response**
1ST Line	Empiric Definitive		Partial Full Resolution
2nd Line	Indications for second line: 1)No response to first line 2)Toxicity to first line 3)Resistant organism		

IX) ANTIVIRAL :

Drug	**Indication**	**Duration**	**Response**

X) IMAGING:

Imaging	Findings	Alteration in management
1)		
2)		

XI) NUMBER OF DAYS OF GCSF :

XII) OUTCOME:

1. Resolution of febrile neutropenia
2. Death

ABBREVIATIONS

- **FN – Febrile Neutropenia**
- **CVC – Central Venous Catheter**
- **CRI – Catheter related infection**
- **CFU – Colony forming unit**
- **MASCC – Multinational Association for Supportive care in Cancer**
- **MRSA – Methicillin resistant staph aureus**
- **IDSA - Infectious Disease Society of America**
- **NCCN - National Comprehensive Cancer Network**
- **IFD – Invasive Fungal Disease**
- **G-CSF – Granulocyte colony stimulating factor**
- **CIA (WIA) - Cancer Institute Adyar (Women India Association)**
- **AIIMS – All India Institute of Medical Sciences**
- **TMH – Tata Memorial Hospital**