Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Mar 07; 10(B):489-500.
https://doi.org/10.3889/oamjms.2022.8446
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Infective Diseases*

Current Sites of Infections and Types of Microorganisms in Patient with Febrile Neutropenia in Hematological Wards – Single Center Study

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Edited by: Ksenija Bogoeva-Kostovska
Citation: Naji A, Sarko S, Atta S. Current Sites of Infections and Types of Microorganisms in Patient with Febrile Neutropenia in Hematological Wards – Single Center Study. Open Access Maced J Med Sci. 2022 Mar 07; 10(B):489-500. https://doi.org/10.3889/oamjms.2022.8446
Keywords: Neutropenia; Hematological malignancies; Leukemia; Lymphoma; Infection; Non-Hodgkin lymphoma
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Received: 29-Dec-2021
Revised: 01-Mar-2022
Accepted: 04-Mar-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Febrile neutropenia occurs in more than 80% of patients with hematological malignances specially after chemotherapy cycles and an infectious source is identified in approximately 20–30%. Various bacterial, viral, and fungal pathogen contribute to the development of neutropenic fever and without prompt antibiotic therapy mortality rate can be as high as 70%.

AIM: The objective of the study was to document the current sites of infection in patients with febrile neutropenia in hematological ward in Baghdad Teaching Hospital, the microorganisms and antibiotic susceptibly in culture positive cases and mortality rate in 1 week and 4 weeks after episode of fever.

PATIENTS AND METHODS: One hundred cases of febrile neutropenia were evaluated in Hematological Ward of Baghdad Teaching Hospital from January 2019 to January 2020. Detailed history, physical examination, and laboratory investigations were conducted and statistical analysis of the results was done.

RESULTS: One hundred cases of febrile neutropenia, mean age of presentation was 41.56 ± 10.5 years. Acute myeloid leukemia (36%) and acute lymphocytic leukemia (26%) were the most common underlying hematological disorder, followed by Aplastic Anemia, Non-Hodgkin Lymphoma, and Hodgkin Lymphoma. Temperature ranged from 38°C to 39°C with mean temperature of 38.4°C and most of the patient presented with short duration of fever, 57% had absolute neutrophil count below 150 cells/μL with mean duration of neutropenia was 14.01 days. Respiratory tract was the most common site of infection (52%) followed by urinary tract (18%) and in 16% had no obvious focus of infection. Thirty percent of cases were culture Gram-positive and Gram-negative microorganism which were more common 62.9% which were generally sensitive to Aminoglycosides while Gram-positive microorganism constituted 29.6% of isolated bacteria and were generally sensitive to vancomycin. No mortality documented 1 and 4 weeks after fever.

CONCLUSION: We concluded that the most frequent sites of infection in patient with febrile neutropenia were respiratory tract followed by urinary tract infection, while 16% had undetermined source of infection. Thirty percent of patients had a positive blood culture with *Escherichia coli* being the most common infecting microorganism, Gram-negative microorganisms were more common than Gram-positive microorganism and fungal infection constituted about 6% of growth. Significant association was found between the fever and longer duration of neutropenia and the greater severity of neutropenia was observed. No mortality related to febrile neutropenia was documented.

Introduction

Fever in neutropenic patients is defined as a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a 1-h period [1]. The definition of neutropenia may vary from institution to institution, but neutropenia is usually defined as an absolute neutrophil count (ANC) <1500 or 1000 cells/μL, severe neutropenia is as an ANC <500 cells/μL or an ANC that is expected to decrease to <500 cells/μL over the next 48 h, and profound neutropenia as an ANC <100 cells/μL. The risk of clinically important infection rises as the neutrophil count falls below 500 cells/μL and is higher in those with a prolonged duration of neutropenia (>7 days) [2].

The ANC can be calculated by multiplying the total white blood cell (WBC) count by the percentage of polymorphonuclear cells and bands [3]. Fever occurs frequently in patients with chemotherapy-induced neutropenia. Factors that contribute to the pathogenesis of neutropenic fever include the direct effects of chemotherapy on mucosal barriers and immune deficits related to the underlying malignancy or other immunosuppressive conditions or therapies. Before the era of empiric antibiotic therapy, infections accounted for most episodes of neutropenic fever and approximately 70% of the mortality in neutropenic acute leukemia patients [4].

Although the majority of patients with neutropenic fever do not have a documented infection, consensus guidelines recommend that all cancer patients with neutropenic fever be promptly evaluated

and treated with empiric broad-spectrum antibiotics [1]. This approach is indicated since it is difficult to distinguish life-threatening infections from less serious infections in this patient population, and infection may progress rapidly in such patients. Furthermore, better outcomes are seen with prompt therapy [5].

An infectious source is identified in approximately 20–30% of febrile neutropenic episodes [1], [6]. Often the only evidence of infection is bacteremia, which is documented in 10–25% of patients [1]. Approximately 80% of identified infections are believed to arise from the patient's endogenous flora [7].

Gram-negative bacilli, particularly *Pseudomonas aeruginosa*, were the most commonly identified pathogens in neutropenic patients until the 1980s [8]. Subsequently, Gram-positive bacteria have become the most common pathogens [9], [10]. Common Gram-positive cocci include *Staphylococcus epidermidis* (by far the most common), *Staphylococcus aureus*, and streptococci; less common Gram-positive organisms include *Corynebacterium jeikeium*, *Bacillus* spp, *Leuconostoc* spp, *Lactobacillus* spp, *Cutibacterium* (formerly *Propionibacterium*) acnes, and *Rhodococcus* spp [11].

A number of changes in practice likely accounted for the trend toward Gram-positive infections, including the introduction of long-term indwelling central venous catheters (CVCs), the use of empiric antibiotic regimens for neutropenic fever designed to cover *P. aeruginosa*, the use of prophylactic antimicrobials that are primarily active against Gram-negative pathogens (e.g., ciprofloxacin), and newer chemotherapeutic regimens [12].

However, more recently, the shift from Gram-negative bacteria to Gram-positive bacteria in documented infections observed during the pre-2000 period has been replaced by a trend back toward Gram-negative bacteria, with the emergence of antibiotic-resistant Gram-negative strains from bloodstream isolates from neutropenic cancer patients [13], [14], [15]. However, the ratio of Gram-positive to Gram-negative bacteria as the cause of bacteremia in cancer patients remains at approximately 60:40 [13], [16].

Fungal pathogens are common in high-risk patients with neutropenic fever but are uncommon in low-risk patients. The risk for invasive fungal infections increases with the duration and severity of neutropenia, prolonged antibiotic use, and number of chemotherapy cycles. Fungi are rarely the cause of the first febrile episode in neutropenic patients [17]. More commonly, invasive fungal infections occur later as a cause of persistent or recurrent neutropenic fever. However, fungal infections can occasionally present early or even before initial chemotherapy. *Candida* spp and *Aspergillus* spp account for most invasive fungal infections during neutropenia. The former is acquired through gastrointestinal tract colonization and translocation across damaged intestinal epithelial surface. The latter are acquired by inhalation of airborne spores (conidia) into the upper and lower respiratory tract followed by germination and invasive hyphal growth. *Aspergillus* spp is a common fungal pathogen in immunocompromised hosts, and infection follows the inhalation of conidia (spores); manifestations primarily affect the lower respiratory tract (pneumonia); and upper respiratory tract (sinusitis) but may also involve the central nervous system, bones, and skin. The agents of mucormycosis can cause life-threatening rhino-orbital-cerebral, pulmonary, and disseminated infections in immunocompromised hosts, particularly those with uncontrolled hyperglycemia due to pre-existing diabetes mellitus or administration of glucocorticoids [18]. *Pneumocystis jiroveci* is a ubiquitous, endogenous fungus that may cause pneumonia in neutropenic patients and in those with defective cell-mediated immunity [19].

Viral infections, especially human herpesviruses, are common in high-risk patients with chemotherapy-induced neutropenia and are effectively prevented with antiviral prophylaxis. Most herpes simplex virus (HSV)-1 and -2 infections in adults are due to reactivation of latent infections in seropositive patients. The likelihood of reactivation is influenced by the intensity of the chemotherapy regimen and by the relative impact upon virus-specific cytotoxic T-lymphocyte-mediated host defenses. Reactivation occurs in two-thirds of seropositive patients undergoing induction chemotherapy for acute myeloid leukemia (AML) and those undergoing hematopoietic cell transplantation in the absence of antiviral prophylaxis [20], [21]. Ulcerations of the oral or esophageal mucosa and ulcers or vesicles of lips, genitalia, skin, or perianal areas are the most common manifestations. HSV can cause a wide variety of syndromes, including encephalitis, meningitis, myelitis, esophagitis, pneumonia, hepatitis, erythema multiforme, and ocular disease [20].

Herpes zoster, which is caused by varicella-zoster virus, often presents in an atypical disseminated pattern involving multiple dermatomes or widespread skin dissemination in immunocompromised hosts. The reported median time to reactivation of herpes zoster in lymphoma patients has been approximately 5 months following initiation of chemotherapy (range: 0.4–51.3 months). Immunocompromised patients with disseminated varicella-zoster virus infection can have pulmonary involvement and should be placed on respiratory precautions to prevent aerosolized transmission to susceptible individuals [22].

Respiratory syncytial virus and influenza virus are important pathogens causing respiratory illness in stem cell transplant recipients in the winter months [23]. Virus-associated hemorrhagic cystitis caused by BK virus and adenovirus is common among hematopoietic stem cell transplant recipients [24].

Rates of *Mycobacterium tuberculosis* infection are high among patients with hematologic malignancy

worldwide, and tuberculosis should be ruled out in neutropenic patients with lung infiltrates who have tuberculosis risk factors [25]. All patients should undergo a careful history and detailed physical examination as well as laboratory, microbiology, and imaging studies. Because symptoms and signs of infection are attenuated due to the lack of an inflammatory reaction, fever may be the sole sign of infection. Thus, it is important to recognize that the absence of the typical symptoms, signs, or laboratory findings suggestive of infection typically seen in non-neutropenic patients cannot be used to exclude the possibility of infection. The evaluation should be performed promptly [26].

A thorough general physical examination should be performed. The emphasis should be on sites most likely to be infected, including the skin, catheter sites, biopsy and bone marrow aspirate sites, teeth, oropharynx and gingival surfaces, sinuses, lungs, abdomen, genitals, and perianal area. In the absence of neutrophils, signs of inflammation can be extremely subtle. Review of systems and a physical examination should be repeated daily. In patients with persistent fever, new sites of infection (e.g., lungs, skin, and urinary tract) may become apparent over time. In addition, as the neutrophil count recovers, localizing symptoms and signs of infection often become evident for the 1st time [26].

The lungs are a common site of infection in patients with chemotherapy-induced neutropenia and should be examined for signs of pneumonia (e.g., rales). Hypoxia, tachypnea, and increased work of breathing are other signs of pneumonia. An abdominal examination should be performed to evaluate for peritoneal signs and/or abdominal tenderness, which may represent neutropenic enterocolitis or *Clostridioides* (formerly *Clostridium) difficile* colitis. Even when an abdominal process is present, abdominal signs may be subtle or absent in neutropenic patients. All IV catheter sites, especially CVC sites, should be carefully examined for subtle signs of infection; slight erythema or tenderness may be the only evidence of a serious “tunnel” infection. The skin and mucous membranes should be examined for signs of erythema, rash, cellulitis, ulcers, furuncles, vesicles, paronychia, mucositis, dental or peritonsillar cellulitis, perianal fissures, and pilonidal disease. The perianal examination should also include inspection of the perianal area. Erythema, pain on palpation, and tender hemorrhoids are important signs of infection. However, digital rectal examination (and rectal temperatures) should be avoided so that one does not introduce infection by traumatizing the fragile mucosa [26].

Laboratory evaluation should include a complete blood cell count with differential, hepatic transaminases, bilirubin, electrolytes, serum creatinine, blood urea nitrogen, serum lactate, urinalysis, and cultures. In interpreting laboratory results in neutropenic patients, it is important to recognize that the absence of the typical laboratory findings suggestive of infection that are usually seen in non-neutropenic patients cannot be used to exclude the possibility of infection. Therefore, absence of abnormalities, such as cerebrospinal fluid (CSF) pleocytosis, pyuria, or neutrophils on sputum Gram stain, does not rule out infection [1].

Specimens for the microbiology laboratory should include at least two sets of blood cultures, specimens should be obtained from other sites as clinically indicated (e.g., sputum, urine, CVC exit site, CSF, skin, and stool). It is important to note, however, that chest radiograph findings are often minimal or absent, even in patients with pneumonia or pulmonary nodules. Intermediate- or high-resolution chest computed tomography (CT) is much more sensitive for detecting abnormalities in neutropenic patients. CT scanning of other sites (head, sinuses, and abdomen/pelvis) should be performed according to suggestive symptoms or other risk factors [1].

Patients presenting with evidence of severe sepsis (sepsis syndrome with end-organ dysfunction) should be regarded as high risk and managed with intravenously administered initial empiric antibacterial therapy and hospitalization. Patients with evidence of septic shock should be managed in a critical care hospital environment based on goal-directed therapy [27].

The guidelines of the Infectious Diseases Working Party of the German Society of Hematology and Oncology and the Northern Ireland Cancer Network recommend that empiric broad-spectrum antibacterial therapy be initiated immediately after blood cultures have been obtained and before any other investigations have been completed in all patients with neutropenic fever [28], [29]. International guidelines advocate the administration of empiric antibacterial therapy within 60 min of presentation in all patients presenting with a neutropenic fever [27], [29], [30].

Early studies of patients with neutropenic fever documented mortality rates of up to 70% if initiation of antibiotics were delayed [31]. The successful management of neutropenic fever and sepsis syndromes is a time-dependent process analogous to acute stroke or ST-segment elevation myocardial infarction syndromes [29].

The febrile neutropenic patient who is developing neutropenic fever or sepsis syndrome may seek medical attention with nonspecific symptoms [32] and may manifest muted signs of an inflammatory process [33]. The aim of empiric therapy is to cover the most likely and most virulent pathogens that may rapidly cause serious or life-threatening infection in neutropenic patients [1]. Initial regimen selection should be guided by the patient’s history, allergies, symptoms, signs, recent antimicrobial agent use and culture data, and awareness of the susceptibility patterns of institutional nosocomial pathogens [34].

The Infectious Diseases Society of America recommends the following approach for the initial

therapy of high-risk neutropenic patients with fever, initiation of monotherapy with an antipseudomonal beta-lactam agent, such as cefepime, meropenem, imipenem-cilastatin, or piperacillin-tazobactam. Other antibiotics (e.g., aminoglycosides, fluoroquinolones, and/or vancomycin) may be added to the initial regimen in patients with complicated presentations (e.g., hypotension and/or mental status changes), focal findings (e.g., pneumonia or cellulitis), or if antimicrobial resistance is suspected or proven. Vancomycin (or other agents that target Gram-positive cocci) is not recommended as a standard part of the initial regimen but should be added in certain patients, such as those with suspected catheter-related infection, skin or soft tissue infection, pneumonia, or hemodynamic instability [1].

Preferred empiric oral antibacterial regimen for low-risk patients not receiving fluoroquinolone-based prophylaxis and who are not known to be colonized by extended-spectrum beta-lactamase-producing gram-negative bacilli involves a combination of ciprofloxacin 750 mg orally twice daily and a beta-lactam agent, such as amoxicillin-clavulanic acid (500 mg/125 mg orally 3 times daily or 1000 mg/250 mg orally twice daily) [1], [2], [35]. Levofloxacin 750 mg orally once daily can be used as an alternative to ciprofloxacin (in combination with amoxicillin-clavulanate), but the ciprofloxacin-containing regimen is favored because the added Gram-positive activity of levofloxacin compared with ciprofloxacin is not necessary when amoxicillin-clavulanate is used [36].

Objectives

We did this study with the aim of:

1. Documenting the current sites of infection in patients with febrile neutropenia in hematological ward in Baghdad teaching hospital
2. The microorganisms and antibiotic susceptibly in culture positive cases
3. The mortality rate in patient with febrile neutropenia in 1 week and 4 weeks after the episode of fever.

Patients and Methods

Study design and sample

This is a prospective observational study. It was conducted at the hematological ward of Baghdad teaching hospital during the period from January 2019 to January 2020. It included 100 patients who have been admitted to the hematological ward because of neutropenic fever.

Procedure and measurement

After taking a verbal consent from the patient, demographic data (age and gender), detailed history including the chief complaints, the underlying disease, onset of symptoms and duration of neutropenia with symptoms that may relate to an underlying site of infection (Cough, Sinuses Pain, Pain at Cannula Site, diarrhea and dysuria, perianal pain) was obtained. All patients were examined looking for potential Foci of infection and they were sent for appropriate investigations including total WBC count and differential count, ANC, hemoglobin level, platelets count and the results were recorded in a questionnaire forum. Sputum, urine and stool examination and imaging studies were performed when clinically indicated and findings were documented.

Samples for culture were collected for all patients (blood, urine, sputum, stool, and catheters), blood samples were drawn under strict aseptic techniques in BACTEC bottles, inoculated on MacConkey agar plates at microbiology laboratory. The plates were inoculated at 37°C for 24 h, isolates were identified and tested for antimicrobial susceptibility using VITEK system. Patients received empirical treatment after admission according the local protocols generally a combination of an aminoglycoside (amikacin) and meropenem was used in most of the cases and in the rest miscellaneous antibiotics included vancomycin, Piperacillin/Tazobactam when clinically indicated such as signs of skin infection, hemodynamic instability until the results of blood culture and antibiotic sensitivity became available and antibiotics were changed according to the laboratory results of the culture and clinical response to the antibiotics.

In those with fever persisted after 5 days of initiation of empirical antibacterial therapy and the patient was still neutropenic, an antifungal agent, Conventional Amphotericin B was added to the antibiotic regimen. Patients were followed up for mortality at 1 week and 4 weeks after the onset of febrile neutropenia episode. The most common sites of infection in febrile neutropenic patient were analyzed, and the most common causative pathogens in the culture-positive cases were also studied.

Inclusion criteria

Age more than 14 years old was included in the study.

Exclusion criteria

Fever occurring during or within 12 h of transfusion of blood and blood products which responded to anti-pyretic were exclude from the study.

Definitions

- Neutropenia: Neutropenia is defined as an ANC of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 h [1]
- Febrile Neutropenia: Neutropenia is defined as a single oral temperature measurement of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a 1-h period in patient with neutropenia [1].

Statistical analysis

Descriptive data were expressed as percentage, median, mean, and standard deviation. Logistic regression model was designed to evaluate the association between the development of severe infection with the duration and severity of neutropenia. T test was used to compare continuous variables and Chi-square test was used to compare categorical variables. Statistical analyses were done using Statistical Package for the Social Sciences (SPSS) for Windows (SPSS for Windows Version 22. Chicago, Illinois). $p < 0.05$ was considered significant.

Ethical statement

This was an observational study, during which patient's health, safety, and privacy were not harmed.

Results

During the study period, 100 patients with febrile neutropenia who were admitted to the hematology unit were evaluated at admission, 1 week and 4 weeks later.

Demographic data

One hundred patients were involved in this study. Febrile neutropenia occurred in 24% (15–20 years) with mean age of presentation of 41.56 ± 10.5 years. 56 patients were male and 44 patients were female with M: F ratio 1.3:1. Age and gender distribution is shown in Table 1.

Table 1: Age and gender distribution of neutropenic fever

Age group	Male	Female	Total
15–19	13	11	24
20–29	10	8	18
30–39	9	7	16
40–49	8	6	14
50–59	7	5	12
60–70	7	5	12
>70	2	2	4

Underlying hematological disorder

Regarding the underlying hematological disorder, 36% had AML, 26% had acute lymphocytic leukemia (ALL), 20% had aplastic anemia (AA), 10% had Non-Hodgkin lymphoma, 4% had Hodgkin Lymphoma, and 4% had multiple myeloma as shown in Table 2.

Table 2: Clinical picture of respondents based on hematological disorder, duration of fever, neutropenia, and site of infection

Hematological disorder		Duration of fever		Neutropenia		Duration of Neutropenia		Site of infection	
AML	36	<1 Week	50	ANC (500–150)	43	7 days	30	Respiratory	52
ALL	26	2 Weeks	30	ANC <150	57	14 days	42	Urinary	18
AA	20	3 Weeks	12			21 days	13	Peri-anal	16
NHL	10	4 Weeks	8			28 days	15	Gastrointestinal	12
HL	4							Sinusitis	12
MM	4							Mucocutaneous	12
								Genital	4
								No focus identified	16

AA: Aplastic Anemia, ALL: Acute lymphocytic leukemia, AML: Acute myeloid leukemia, HL: Hodgkin's lymphoma, NHL: Non-Hodgkin lymphoma, MM: Multiple myeloma, ANC: Absolute neutrophil count.

Fever

Most of our patient had low grade fever and mean temperature was 38.4°C ranging from 38°C to 39°C. Most of the patient presented with short duration of fever, 50% had fever of <1 week, 30% had fever for 2-weeks, 12% had fever for 3 weeks, and 8% had fever for 4-weeks with median duration of fever 12.9 ± 8.89 days.

Neutropenia

About 43% presented with ANC level between (500 and 150) while 57% of them had neutropenia below 150, with mean of 161.2. Regarding duration of neutropenia, 30% had neutropenia for 7 days, 42% had it for 14 days, 13% for 21 days, and 15% for 28 days, the mean duration of neutropenia was 14.01 ± 9.65 days.

Site of infection

Regarding the site of infection of in this study, 52% had evidence suggestive of respiratory tract infection (productive cough, chest crepitation, bronchial breathing, imaging findings of infection, and sputum culture), 18% had evidence suggestive of urinary tract infection (dysuria and loin pain, renal angle tenderness, general urine examination and urine culture), 16% had peri-anal abscess, 12% had evidence of sinusitis (tender sinuses, rhinorrhea, and radiological evidence of sinusitis), 12% has had evidence of Gastro-Intestinal Infection (diarrhea and general stool examination), 12% had evidence of mucocutaneous infections (local abscess, mucositis, cellulitis, and canula site infection), 4% had evidence of genital infection (vaginal and urethral discharge), and 2% had evidence of Central Nervous System infection (headache, DLOC,

focal neurological signs, and CSF analysis), Table 2 illustrated the sites of infections. In 16% of patients, no obvious focus of infection was found despite thorough clinical and laboratory evaluation.

Culture and sensitivity

Only 30% of patients were culture positive (blood, urine and sputum, catheter, and stool), while 70% had no growth of bacteria as shown in Table 3 and the most common isolated microorganism was *Escherichia coli* 46% followed by *S. aureus* 13%, *Streptococcus viridans* 13%, *P. aeruginosa* 13%, *Acinetobacter* species 3%, and micrococci 3%, while fungi isolated in 6% of culture positive patients. Gram-negative microorganisms were more common 62.9% while Gram-positive microorganism constituted 29.6% of isolated bacteria.

The antimicrobial susceptibility profile of all Gram-negative organism is described in Table 4, overall sensitivity of Gram-negative organism were 76.1% sensitive to aminoglycosides, 61.9% sensitive to carbapenems, 31.1% sensitive to cephalosporins, 26.1% sensitive to piperacillin, 13.1% sensitive to quinolones, and 7.1% sensitive macrolides. Among *E. coli* which was the most frequently isolated microorganism, 85.7% of growth were sensitive to carbapenems, 78.5% of growth were sensitive to aminoglycosides, 28.5% of growth were sensitive to piperacillin, 21.5% of growth were sensitive to macrolides, and 14.3% were sensitive to both quinolones and cephalosporins.

Table 3: Types of bacteria isolated from 30 culture of patients with febrile neutropenia

Microorganism group	Microorganism isolated	No. of growth	Percentage
Gram-negative 63.3% (19)	*Escherichia coli*	14	46.7
	Pseudomonas aeruginosa	4	13.3
	Acinetobacter	1	3.3
Gram-positive 30% (9)	*Staphylococcus aureus*	4	13.3
	Streptococcus viridans	4	13.3
	Micrococci	1	3.3
Fungi 6.7% (2)	*Aspergillus*	2	6.7

Resistance to carbapenems and macrolides was detected in 100% of pseudomonas isolates, 75% of the strains were resistant to quinolones and cephalosporins including ceftazidime, and 50% of them were resistant to both aminoglycosides and piperacillin. One culture revealed the growth of *Acinetobacter* which was sensitive to aminoglycosides and carbapenems, and resistant to all other antibiotic groups.

The antimicrobial susceptibility of Gram-positive organism is described in Table 4, overall, 100% of them were sensitive to vancomycin. *S. aureus* was isolated in 4 cultures and shows 100% sensitivity to vancomycin and quinolones, 100% resistant to piperacillin and macrolides, and 50% sensitivity to cephalosporins. *S. viridans* showed 100% sensitivity to vancomycin, 100% resistant to piperacillin, quinolones, macrolides, and 50% resistant to cephalosporins. Micrococci were detected in one growth and it was resistant to all tested antibiotics.

Statistical analysis by logistic regression model was designed to evaluate the association between the development of neutropenic fever and the severity of neutropenia (ANC level), duration of neutropenia (in weeks). Results show significant association between the development of neutropenic fever and the longer duration of neutropenia (2-weeks and longer) (Odd ratio 0.85, $p < 0.0001$) and with lower levels of ANC <150 (odd ratio 1.04, $p < 0.0001$).

No significant association was found between the duration of neutropenia and the site of infection nor with the type of microorganism as shown in Table 5.

Mortality

No mortality related to neutropenic fever was documented during the 1 week and 4 weeks follow-up.

Discussion

In this study, we evaluated the sites of infection in patients with febrile neutropenia, the causative microorganisms in the culture-positive cases and their antibiotics sensitivity, the mortality rate and outcome of patients and the association between the development of neutropenic fever and the duration of neutropenia. In this study, there was slight predominance of male (56%) over female (44%) with male: female ratio 1.3:1 similar result was found in a study by Siddiqui *et al*. in which 60% were male with male to female ratio of 1.5:1 [37].

Mean age of patients was 41 ± 10.59 years range (15–75), 24% fell in the range (15–20), Yadegarynia *et al*. found in his study that the mean age of 43.87 ± 17.2 years (ranged 13–88 years) [38] while

Table 4: Antimicrobial susceptibility profile of Gram-positive and Gram-negative organisms

Organism	Cephalosporins (%)	Macrolides (%)	Quinolones (%)	Carbapenems (%)	Aminoglycosides (%)	Piperacillin (%)	Vancomycin (%)
Staphylococcus aureus (4)	S: 2 (50)	S: 0	S: 4 (100)	S:	S: --	S: 0	S: 4 (100)
	R: 2 (50)	R: 4 (100)	R: 0 (0)	R: --	R: --	R: 4 (100)	R: 0
Streptococcus viridans (4)	S: 2 (50)	S: 0	S: 0	S: --	S: --	S: 0 (0)	S: 4 (100)
	R: 2 (50)	R: 4 (100)	R: 4 (100)	R: --	R: --	R: 4 (100)	R: 0
Micrococci (1)	S: 0	S: 1 (100)	S: 1 (100)	S: --	S: --	S: --	S: 1 (100)
	R: 1 (100)	R: 0	R: 0	R: --	R: --	R: --	R: 0
Escherichia coli (14)	S: 2 (14.3)	S: 3 (21.5)	S: 2 (14.3)	S: 12 (85.7)	S: 11 (78.5)	S: 4 (28.5)	S: --
	R: 12 (85.7)	R: 11 (78.5)	R: 12 (85.7)	R: 2 (14.3)	R: 3 (21.5)	R: 10 (71.5)	R: --
Pseudomonas aeruginosa (4)	S: 1 (25)	S: 0	S: 1 (25)	S: 0	S: 2 (50)	S: 2 (50)	S: --
	R: 3 (75)	R: 4 (100)	R: 3 (75)	R: 4 (100)	R: 2 (50)	R: 2 (50)	R: --
Acinetobacter (1)	R	R	R	S: (100)	S (100)	R	---

Table 5: Results of logistic regression model to evaluate the association between neutropenic fever with duration and severity of neutropenia, with site of infection and with type of microorganisms

Variable	Odd ratio	Confidence Interval 95%	p-value
Duration of neutropenia>2 weeks	0.85	0.7–0.82	<0.0001
Absolute neutrophil count level<150	1.04	-0.332–2.412	<0.0001
Respiratory tract infection and duration of neutropenia	0.6891	-1.5472–2.8654	0.4848
Peri-anal infection and duration of neutropenia	1.2	0.5–1.9	0.7324
Sinusitis and duration of neutropenia	0.9737	-0.4122–2.3596	1
Gastrointestinal infection and duration of neutropenia	0.627	-0.905–2.159	0.4
Urinary tract infection and duration of neutropenia	1.1169	0.7469–1.4869	0.8296
Escherichia coli and duration of neutropenia	0.7645	0.6214–2.15	0.5978
Streptococcus viridans and duration of neutropenia	1.2211	0.0895–2.3527	0.7143
Pseudomonas aeruginosa and duration of neutropenia	1.5353	0.4037–2.6669	0.4459

Hassan *et al*. reported that the incidence of neutropenia was predominant among individuals aged 65 years or more compared to younger than 65 years of age [39] and explained his findings by the fact that Neutropenia is more common among the older age group (65 years and more) because their ability to produce mature neutrophil is reduced and recommend to reduce the dose of chemotherapy and the administration of granulocyte colony-stimulating factor should be increased in older age group. ALL and AA are mainly diseases of young age group and AML seen in younger age group of Iraqi population, those three forms the majority of cases in this study.

In this study, neutropenic fever occurred most in patients with AML (36%) followed by ALL and AA (26% and 20%, respectively), this finding is similar to many other studies including a study by Mucahit *et al*. [40] in which AML constituted 32% of the cases followed by ALL (20%). There are many explanations to the high rate of neutropenia within AML patients, one of the causes of neutropenia is that the expansion of one clone of WBC will prevent other white cells from proliferating and will result in neutropenia, other causes involve AML treatments which is myeloablative and target the immune system and the number of neutrophils will furtherly depleted [41].

The mean duration of fever was 12.9 ± 8.89, the mean ANC at the onset of fever was 161.2, and the mean duration of neutropenia was 14.01 ± 9.65. Karimi *et al*. in her study showed that median duration of neutropenia was 4 days, and the median duration of febrile episodes was 1 day [42]. The number of days from onset of fever to the lowest ANC count was 2 ± 1.8 days in a study by Hosiriluck *et al*. [43] A low-neutrophil count and a protracted neutropenia (0.5×10^9/l for 10 days) are major risk factors for infection. A duration of neutropenia of more than 5 weeks is associated with an incidence of infection close to 100% [44].

Regarding the most common sites of infection in this study, the most common were Infections of the respiratory tract (52%) followed by infection of the urinary tract (18%), Mucahit *et al*. in his study explained that lung infections were important cause of fever in neutropenic patients with ranges about 22% [40]. Alterations in the composition of the oropharyngeal flora, damages of respiratory and gastrointestinal mucosa due to chemotherapy and aspiration have important roles in the development of pneumonia and also in our crowded wards, pathogens can spread easily and rapidly between the patients. Urinary tract infections accounted for 18% of infections followed by peri-anal abscess (18%), sinusitis (12%), gastroenteritis (12%), and mucocutaneous infections (12%). In a study by Sickles *et al*. explained that the most common infection in order of frequency were pharyngitis, skin infection, pneumonia, anorectal infection, and urinary tract infection [33].

Blood cultures are the cornerstone of diagnostic workup of febrile neutropenia, as they provide identification of the causative organisms and susceptibility pattern but their sensitivity is reduced significantly once antimicrobial therapy has been started. In this study, only 30% of our patients had positive culture from different sites. Blood cultures are positive in about 20% and 30% of cases in Hughes *et al*. and Lyman and Rolston studies [45], [46]. Meidani *et al*. in Iran performed their study on neutropenic patients with fever, they found 68.4% of medical documents with no result for culture of any body fluid and only 2.6% of patients had positive blood culture [47], and this is consistent with the results of Bouafia et al. study in which the percentage was slightly lower (24.1%) [48].

In the cultures with positive growths that were found in this study, Gram-negative bacteria were more common than Gram-positive bacteria (62.9% vs. 29.6%). Previously, Gram-positive bacteria used to account for 60–70% of microbiologically proven infections, which may in part be due to the wide use of quinolones as prophylactic antibiotics and the use of broad-spectrum empirical antimicrobial therapy against gram negative bacteria, other possible causes of this change include widespread use of intravenous catheters and Central-Venous lines, together with more profound and prolonged neutropenia due to intensive and repeated cycles of chemotherapy regimens [49]. However, there was increase in the Gram-negative bacteria in the EORTIC-IATG trial of empirical antibiotic therapy in neutropenic patient from 6.5% to 12% ($p < 0.001$). The cause of increment in Gram-negative bacteria is not clear, it could be either to decreased use of quinolone prophylaxis or high rate of resistance. However, the increase in the Gram-negative proportion was also documented in health-care centers in which ciprofloxacin still used and in those whom had never used it [50]. Gram-positive cocci were isolated in 34.61% while Gram-negative bacilli were identified in 61.53% in a study by Mandal *et al*. [51]. Fungal infections in form of aspergillosis accounted for 6% of febrile neutropenic patients in this study, similar result found in a study by Sönmez *et al*. [52] in which aspergillosis accounted for 5.9%.

Among Gram-negative bacteria, *E. coli* was found to be the most common culprit pathogen (46.6%) Gaytán-Martínez *et al*. found that *E. coli* was the pathogen isolated mostly during episodes of primary bacteremia among patients with cancer and febrile neutropenia [53]. The major source of *E. coli* bacteremia is bacterial translocation across the gastrointestinal tract, mucosal barrier injury allows bacterial translocation which has been proved to increase the incidence of bacteremia. Mucositis caused by chemotherapy or by irradiation, along with the prophylaxis with either Fluoroquinolones or trimethoprim-sulfamethoxazole are considered the most important risk factors for bacteremia. It has been recently demonstrated that mucositis, rather than prolonged neutropenia, was responsible for a high rate of bacteremia in neutropenic patients [54].

In fact, in 2000 Gram-positive bacteria accounted for 76% of all bacteremia in cancer patients in the United States [9]. However, this has no longer being the case because the Gram-negative bacteria becoming more frequent than Gram-positive in many health-care centers. According to a questionnaire survey performed among hematology centers from Europe participating in the European Conference on Infections in Leukemia in 2011, *Enterobacteriaceae* were isolated in approximately 30% [55] Similarly, in a recent systematic review on febrile neutropenic patients, blood cultures were positive for Gram-negative rods in a percentage ranging from 25% to 74% (mean 50%) and *E. coli* was the most frequently isolated pathogen [15]. There are even cohorts in which Pseudomonas species and *Acinetobacter* species were responsible for 43% of all sepsis episodes [56]. In a study by Ramzi *et al*., 31% were diagnosed as pseudomonas infection [57]. Recently in some health-care centers, drug-resistant Gram-negative bacteria such as *Acinetobacter baumannii*, multidrug-resistant (MDR) *P. aeruginosa*, extended-spectrum beta-lactamase-producing Gram-negative bacteria, and carbapenemase-producing Gram-negative bacteria have become the causative agents of an increasing number of infections which may provide explanation to the fact the Gram-negative bacteria are returning to be a significant cause of bacteremia in febrile neutropenic patients because the standard treatment has increase in the resistance rate [58], [59].

MDR Gram-negative bacteria are defined as organisms with resistance to at least three of the following antibiotic classes: Antipseudomonal penicillin, cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones [60]. In this study, *E. coli* showed widespread resistance to cephalosporins (85.7% of isolated growths were resistant), quinolones (85.7% were resistant), and piperacillin (71.5% were resistant) which fit the definition of MDR strain. *E. coli* still having good sensitivity to aminoglycosides (78.5%) and carbapenems (85.7%). In many centers, *E. coli* are no longer susceptible to cephalosporins, and, in some cases, the lack of drugs active against carbapenem-resistant Gram-negative rods led clinicians to turn to combination therapies based on old, more toxic agents such as polymyxins. Moreover, the benefit of the prophylaxis with fluoroquinolones in settings with high fluoroquinolone-resistance rates has been questioned. Health-care costs increased in case of infections with resistant bacteria due to prolonged hospitalization and expensive antibiotic treatments [61].

P. aeruginosa is being increasingly resistant to ciprofloxacin. It was 75% in this study and 50% in a study by Farhan *et al*. [62] extensive use of ciprofloxacin as a prophylactic antibiotic in cancer patients receiving chemotherapy is likely associated with this change. Therefore, it is suggested that in our setting, ciprofloxacin should not be the antibiotic of choice for bacterial infections prophylaxis. In this study, *P. aeruginosa* had 100% resistance to carbapenem, 75% resistance to cephalosporins including the antipseudomonal ceftazidime, and 50% resistance to piperacillin while being 50% sensitive to aminoglycosides agents.

In recent years, an increasing proportion of infections in neutropenic patients are caused by organisms which have multidrug resistance; in this study, *Acetobacter* is one of them which is universally resistant to cephalosporins, macrolides, and quinolones but still sensitive to meropenem [63]. There is a worrisome decrease in the sensitivity rates to the main antibiotic drugs among Gram-negative bacteria compared to what has been reported in more recent studies, which have been recently reviewed [64].

Regarding antimicrobial susceptibility among Gram-positive bacteria, we found that the isolates of *S. aureus* were 100% sensitive to vancomycin, 100% sensitivity to quinolones, 50% *in vitro* sensitivity to cephalosporins, and 100% resistant to macrolides and piperacillin. *S. viridans* were also 100% sensitive to vancomycin but totally resistant to quinolones, macrolides, piperacillin, and 50% sensitive to cephalosporins.

As immediate empirical antibiotic therapy at the onset of fever in neutropenic patients is critical, current data on the local epidemiology of predominant microorganism and the patters of their resistance patterns should be taken into consideration for appropriate empirical treatment strategies [1], [11], [58]. However, interregional spread of resistant strains did occur, on the other hand, there are still regions where resistant strains are infrequent and low mortality rate with blood stream infection is documented [65]. Therefore, local epidemiological data that are updated continuously are crucial. Very low neutrophil counts are risky for infection and the risk increases manifold when ANC is <500 cells/μL. Longer duration of neutropenia is associated with longer stay in the hospital, greater risk of acquiring hospital infections, longer duration of Intravenous lines, parenteral nutrition, higher risk of loss of mucosal integrity, use of several antibiotics, and development of drug-resistant clones [66].

No mortality rate in this study has been documented, which may be related to the small sample number in this study and decreasing the mortality of neutropenic infections in the recent years as it ranged from 24.5% in study of Velasco *et al*. in 2003 [67] to 9.5% in a study by Kuderer *et al*. in 2006 [68] to 3.35% in a study by Nordvig *et al*. in 2018 [69]. It appears that the mortality rate and infectious condition have a decreasing trend during recent years. Improved outcomes have resulted from prompt usage of antibiotic therapy and prophylaxis.

Conclusions

We concluded that:

1. The most frequent sites of infections in patients with febrile neutropenia were respiratory tract followed by urinary tract infection, while 16% had no obvious source of infection
2. Thirty percent of patients had a positive blood culture with *E. coli* being the most common infecting microorganism, Gram-negative microorganisms were more common than Gram-positive microorganism, and fungal infection constituted about 6% of growth
3. Significant association was found between the fever and longer duration of neutropenia and the greater severity of neutropenia was observed
4. No mortality related to febrile neutropenia was documented.

Recommendations

1. Infection control programs are mandatory in every cancer center. In addition to these it should be kept in mind that infection control procedures including hand hygiene, standard barrier precautions, chlorhexidine bathing and nasal decolonization, private rooms and patient isolation, and not allowing plants and dried or fresh flowers into patient rooms may be effective means for preventing infections and transmissions
2. Antibiotics stewardship including regular reports of the sensitivity patterns, knowledge of local epidemiology, optimizing the use of antibiotics (right dose and right choice), and avoiding long term treatment courses
3. In patient who is at high risk of infection with MDR bacteria, de-escalation approach has been proposed to which start antibiotic which cover most probable strain and narrow it after 72 h if no MDR pathogen isolated.

Limitations

1. This study was a single-center study
2. The short study period and small size of sample observed
3. No post-discharge surveillance was undertaken, which can underestimate the incidence because infections with long incubation periods can be missed.

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