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Screening of Some Bacterial and Fungal Infections in Neutropenic Cancer Patients in Al-Najaf Governorate, Iraq

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ABSTRACT

Aims Infection is one of the most important complications of neutropenia and contributes to the high rate of morbidity and mortality. This study aimed to investigate some bacterial and fungal infections in cancer patients with neutropenia.

Materials & Methods 110 specimens from 10 normal humans as a control group and 100 specimens from neutropenic cancer patients were collected. The ELISA technique was used to assess the presence of neutropenia in patients. The diagnosis of bacterial infections was based on the bacteriological culture of isolated specimens (blood, sputum, and urine) and biochemical test, then Vitek-2 Compact.

Findings 60 specimens (60%) contained an infection. 44 samples (73.3%) had positive blood cultures, consisting of 25 (41.6%) in leukemia patients and 19 (31.7%) in breast cancer patients. 6 samples (10.0%) of bladder cancer patients had positive urine cultures. Positive sputum was seen in 10 samples (16.7%) of patients with lung cancer, while the cultures of 40 samples (40.0%) were negative. Ten E. coli (16.7%) was in patients with leukemia and bladder cancer, 15 *Pseudomonas aeruginosa* (25.0%) in patients with breast cancer and leukemia, and 25 *Klebsiella pneumonia* (41.7%) in the patients with leukemia, breast cancer, and bladder cancer. However, samples from patients with lung cancer contained 4 coagulase-positive Staphylococci (6.7%) and 6 *Streptococcus pneumoniae* (10.0%).

Conclusion Neutropenia is more common in leukemic patients. Gram-negative bacteria are the greatest public bacteria isolated in the patients. *Klebsiella pneumonia* and Streptococcus pneumonia are the most common Gram-positive bacteria. All types of bacteria are resistant to most antibiotics.

Keywords Neutropenia; Cancer; Chemotherapy; Infections; Antibiotics

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Introduction

Neutrophils or Polymorphonuclear Neutrophils (PMN) are the largest type of white blood cells (60-70% in adults). These cells originate from bone marrow stem cells. It is one of the greatest main forms of phagocytes in the immune system, where it responds to chemical stimuli. Neutrophils attached to epithelial cells travel from the blood to the tissues and the locations of infection [1]. Neutrophils play a critical role in the acute inflammatory response and host defenses against bacterial infections [2]. The microorganisms inside the vacuole are devoured by the phagosome, which combines with lysosomes to break down the microbes. The Absolute Neutrophil Count (ANC) is the product of the total number of white blood cells and the percentage of neutrophils and cell bunds detected in the peripheral blood by the differential number of white blood cells [3].

Neutropenia, a deficiency of these cells, predisposes to infection, chiefly by organisms resident on body surfaces. The risk of infection is greatest with severe neutropenia, defined by an absolute blood neutrophil count less than 0.5×10^9/L [2]. A decrease in the number of white blood cells or neutropenia is a condition characterized by an abnormally low number of neutrophils in the blood circulation. Neutropenia is defined as a decrease in ANC of less than 1500 cells/mm^3 in most children and adults. Neutropenia is divided into mild, moderate, and severe degrees, whose percentage is 1000-1500 cells/mm^3, 500-1000 cells/mm^3, and <500 cells/mm^3, respectively [4].

Cancer is one of the most diseases that researchers have studied for several decades. It is an important cause of death, with a prevalence of > 10 million deaths per year [5]. Cancer is abnormal body cells that divide without control and can spread to nearby tissues. Human cells that have been attracted by cancer and, to some extent, changed into pathogenic organisms or tumor-forming components are destructive agents [6, 7]. Traditionally, cancer patients are treated with surgery, chemotherapy, radiation, immunotherapy, targeted therapy, or hormonal therapy [8].

The most common cause of neutropenia in cancer patients is the side effects of chemotherapy. Chemotherapy that stimulates neutropenia increases the risk of infection and impairs the treatment of cancer. Neutropenia may be inhibited by white blood cell growth factors. To deter neutropenia, the patient is allowed to take arranged treatment to decrease the danger of infection and hospitalization [9].

As we know, chemotherapy act to attack, quickly separating cells in the body, especially cancer cells that are dividing rapidly. In addition, chemotherapy cannot distinguish between cancerous cells and healthy cells that divide rapidly, such as bone marrow cells. Therefore, several chemotherapy patients, particularly the elderly, experience a decrease in blood cells, including white blood cells, which fight infections [10]. This causes patients to stop or reduce chemotherapy until the white blood cell count rises enough to restart treatment, which can cause cancer and random cell growth. A decrease in white blood cell count may increase the patient's risk of infection, which may lead to delayed treatment or hospitalization [11].

Infection is one of the most important complications of neutropenia and contributes to the high rate of morbidity and mortality. This infection includes the bloodstream and the lower respiratory tract. In patients with neutropenic fever, the rate of bloodstream attack has been reported between 11% and 38% [12]. Although fever is an indicating sign, patients can come with normal temperature or even hypothermia [13]. The average number of complications related to Febrile Neutropenia (FN) is roughly 25% to 30%, and the mortality rate is as high as 11% in some groups [14]. In addition, hospital and admission mortality could reach 50% in severe and septic shock [13].

The description of infectious events in neutropenic patients is extremely important. Knowledge about these events in this population helps to reduce costs and to adapt published data to the reality of the institution, permits continuous improvement of the service offered, and maximizes the benefits of treatment [15]. However, clinical manifestations of infections due to neutropenia may be mild or even absent, a situation that complicates diagnosis, initial treatment, and the follow-up of patients with febrile neutropenia [16, 17].

The range of organisms associated with infection in neutropenic patients changes from Gram-positive to Gram-negative bacilli with the increase of predominant cocci pathogens [18]. The incidence of bacteremia with Gram-negative organisms is more than with Gram-positive. *Enterobacteriaceae* sp. is the most predominant, followed by *Pseudomonas aeruginosa* and other Gram-negative. Resistant pathogens, unfortunately, have progressed because of the use of prophylactic antibiotics such as Extended-Spectrum Beta-Lactamase (ESBL). The most important causes of bacteremia among gram-positive organisms are Staphylococcus aureus, including Methicillin-Resistant *Staphylococcus aureus* (MRSA), coagulase-negative Staphylococcus, Streptococcus of the viridans group, and Enterococci, especially Vancomycin-Resistant Enterococcus (VRE) [19]. Fungal infections are not as common as bacterial infections, but they occur by *Aspergillus* sp. and *Candida* sp. [20].

One of the more challenging areas in the febrile neutropenia is the question of diagnosis and therapy of infection [21]. Nowadays, increasing resistance to antimicrobial agents is a recurrence and a big problem [19], which plays a crucial role in the outcome of febrile neutropenia [22].

Increased use of broad-spectrum antibiotics has resulted in resistant bacteria, and different centers have different prevalence and trends of resistance. Therefore, it is important to check the prevalence of microorganisms and their sensitivity pattern to carefully design antibiotic regimens and review the institutional policies regarding the use of empirical antibiotics in patients of febrile neutropenia. Since the 1990s, many studies have been conducted on the prophylactic use of antibiotics to cope with febrile neutropenia [23]. However, on the other hand, according to a study, the prophylactic use of such antibiotics has resulted in resistant strains, and thus it is emphasized that the prophylactic use of antibiotics should be discouraged [11, 23].

The present study aimed to investigate some bacterial and fungal infections in cancer patients who are undergoing chemotherapy and suffering from neutropenia.

Materials and Methods

Collecting specimens

110 specimens from 10 normal humans as a control group and 100 specimens from cancer patients with neutropenia suffering from nosocomial infection and fever and receiving chemotherapy and antibiotic therapy were collected from the Al-Sadar Medical City in Al-Najaf Al-Ashraf during March 2019 to January 2020. The specimens included sputum, urine, and blood from lung, and bladder. In addition, blood samples were taken from all patients for later experiments.

Febrile neutropenia and detection

Blood samples (2mL) were collected from 110 specimens, then 1ml was separated of serum, and initially frozen at -20°C. The enzyme immunoassay was used for the quantitative measurement of Anti-Neutrophil Cytoplasmic Antibodies (ANCA) in human serum by ANCA ELISA Kit (Demeditec Diagnostics GmbH; Germany).

Measurement of some immunological profile

Interleukin (IL)-8, IL-10, and CCL2 (C-C Motif Chemokine Ligand 2) were asssessed using commercially available ELISA kits (Elabscience; USA). Another 1ml of blood of samples were collected in EDTA (Ethylenediaminetetraacetic Acid) tubes for detecting the percentage of neutrophil and WBC (White Blood Cell) count analyses.

Identification of bacteria in samples

Samples were stained with Gram stain to distinguish Gram-positive and Gram-negative bacteria and then cultivated on MacConkey agar (MAC) and Blood Agar (BA) incubated at 37°C for 18-24h. The morphological appearances of the colonies, including size, shape, and color, were noted, and bacterial isolates, including *Staphylococci aureus*, *Streptococcus pneumonia*, *Escherichia coli*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa*, were consequently recognized and measured by biochemical testing [24]. In addition, bacterial isolates were recognized using Vitek-2 Compact (Bio Mérieux; France) and the bacteria sensitive to antibiotics were detected by Vitek-2 antibiotics with the AST-XN05 card (Bio Mérieux; France).

Identification of fungi in samples

• Diagnosis of Invasive Pulmonary Aspergillosis (IPA)

Invasive pulmonary aspergillosis in patient serum was detected using Human Aspergillus Galactomannan Antigen (GM-Ag) ELISA kit (MyBioSource; USA).

• Detection of yeasts and yeast-like organisms

Fresh clinical samples (oral, vaginal, anorectal, urine, stool, and respiratory tract specimens) were got from patients. Tests were obtained from subcultures grown for 24-48h on sabouraud-gentamicin-chloramphenicol agar plates and identified by VITEK 2 system and ID-YST card (Bio Mérieux; France), which involved 64 wells with 47 fluorescent biochemical tests.

Data analysis

All information was collected and analyzed by SPSS 24 software.

Findings

110 samples from 10 normal people were collected as a control group, and 100 samples from cancer patients under chemotherapy and suspected of neutropenia. These patients had nosocomial infection and most of them had fever and were treated with antibiotics.

30 blood samples from patients with leukemia had severe neutropenia depending on ANC and anti-neutrophil levels, and 8 samples from patients with breast cancer had moderate neutropenia, while the number of patients with moderate neutropenia caused by lung and bladder cancer was 4 (33.3%) and 2 (33.3%), respectively. The highest level of ANC and anti-neutrophil was found in breast cancer patients with 0.6×10^9/L and 9.6±0.3%, respectively (Table 1).

Table 1) Frequency distribution of neutropenia, concentration of absolute neutrophils and anti-neutrophils in cancer patients

Cancer type	Total patients	Neutropenia patients	Absolute neutrophil count	Anti-neutrophil level
Leukemia	53	30 (56.6%)	0.4×10^9/L	9.8±0.6%
Breast	29	8 (27.6%)	0.6×10^9/L	9.6±0.3%
Lung	12	4 (33.3%)	0.7×10^9/L	8.5±0.4%
Bladder	6	2 (33.3%)	1×10^9/L	8.7±1.7%
Control	10	-	5000×10^9/L	-

Patients with bladder cancer had higher levels of IL-10, IL-8, and CCL2, followed by lung cancer patients, while lower levels of IL-10, IL-8, and CCL2 were observed in leukemia patients (Table 2).

The frequency of specimens, including blood, sputum, and urine, were distributed between leukemia (53.0%), breast cancer (29.0%), lung (12.0%), and bladder (6.0%), respectively. After

diagnosis by biochemical test and Vitek-2, 60 specimens (60%) contained an infection. 44 samples (73.3%) had positive blood cultures, consisting of 25 samples (41.6%) of leukemia patients and 19 samples (31.7%) of breast cancer patients. 6 samples (10.0%) of bladder cancer patients had positive urine cultures. Positive sputum was seen in 10 samples (16.7%) of patients with lung cancer, while the cultures of 40 samples (40.0%) were negative.

Table 2) Concentration of IL-10, IL-8 and CCL2 in cancer patients

Cancer type	Neutropenia patients	IL-10 level (pg/mL)	IL-8 level (pg/mL)	CCL2 level (pg/mL)
Leukemia	30	8.5±0.8	111.0±8.8	1340.0±61.9
Breast	8	10.5±0.5	120.0±6.5	1359.0±72.7
Lung	4	11.0±0.7	123.0±11.5	1366.0±53.7
Bladder	2	12.0±1.6	128.0±8.4	1380.0±202.2
Control	-	0.5±0.2	10.9±0.8	1566.0±101.7

Ten *E. coli* (16.7%) was observed in patients with leukemia and bladder cancer, 15 *Pseudomonas aeruginosa* (25.0%) in patients with breast cancer and leukemia, and 25 *Klebsiella pneumonia* (41.7%) in the patients with leukemia, breast cancer, and bladder cancer. However, samples from patients with lung cancer contained 4 coagulase-positive Staphylococci (6.7%) and 6 *Streptococcus pneumoniae* (10.0%), in addition to fungal infection (Table 3).

In leukemia patients, two *E. coli* (6.7%) and two *P. aeruginosa* (6.7%) were sensitive to Amikacin, and three *E. coli* (10.0%) and two *P. aeruginosa* (6.7%) were sensitive to Piperacillin/Tazobactam, while *K. pneumonia* was resistant to all antibiotics. In breast cancer patients, two *P. aeruginosa* (25.0%) were sensitive to Levofloxacin, and two *K. pneumonia* (25.0%) were sensitive to Ciprofloxacin. One of the *E. coli* isolates (50.0%) from patients with bladder cancer showed sensitivity to both Cefixime and Ceftriaxone. In lung cancer patients, one of the *Staphylococcus aureus* (25.0%) were sensitive to Imipenem, Azithromycin, and Linezolid, and one of the *Streptococcus pneumonia* (25.0%) were sensitive to both Ciprofloxacin and Levofloxacin (Table 4).

Table 3) Frequency distribution of microorganisms in cancer patients (n=60)

Type of cancer	Specimens	Frequency	Total
Escherichia coli			
Leukemia	Blood	8 (13.4%)	10 (16.7%)
Bladder cancer	Urine	2 (3.3%)	
Pseudomonas aeruginosa			
Leukemia	Blood	10 (16.7%)	15 (25.0%)
Breast cancer	Blood	5 (8.3%)	
Klebsiella pneumoniae			
Leukemia	Blood	7 (11.7%)	
Breast cancer	Blood	14 (23.3%)	25 (41.7%)
Bladder cancer	Urine	4 (6.7%)	
Staphylococci aureus			
Lung cancer	Sputum	4 (6.7%)	4 (6.7%)
Streptococcus pneumonia			
Lung cancer	Sputum	6 (10.0%)	6 (10.0%)

Table 4) Antibiotics sensitivity against different bacteria isolated from cancer patients

Type of cancer	Neutropenia patients	Microorganism	Antibiotic sensitivity	No. (%)
Leukemia	30	*Escherichia coli*	Amikacin	2 (6.7)
			Piperacillin/Tazobactam	3 (10.0)
		Pseudomonas aeruginosa	Amikacin	2 (6.7)
			Piperacillin/Tazobactam	2 (6.7)
		Klebsiella pneumoniae	-	-
Breast cancer	8	*Pseudomonas aeruginosa*	Levofloxacin	2 (25.0)
		Klebsiella pneumoniae	Ciprofloxacin	2 (25.0)
Bladder cancer	2	*Escherichia coli*	Cefixime Ceftriaxone	1 (50.0)
Lung cancer	4	*Staphylococci aureus*	Imipenem Azithromycin Linezolid	1 (25.0)
		Streptococcus pneumonia	Ciprofloxacin Levofloxacin	1 (25.0)

A high level of GM-Ag was observed in neutropenic patients with lung cancer (Table 5).

Table 5) Percentage of GM serum level in cancer patients

Cancer type	Neutropenia patients	Patients with Aspergillosis	GM serum level
Leukemia	30	2 (6.7%)	0.68±0.14
Breast cancer	8	1 (12.5%)	0.71±0.12
Lung cancer	4	2 (50.0%)	0.88±0.14
Bladder cancer	2	0 (0)	0

25 strains of yeasts and yeast-like fungi, including 7 species, were identified with the VITEK ID-YST card. The strains were isolated from clinical samples (oral, vaginal, anorectal, urine, stool, and respiratory tract specimens).

The tests were performed using 24-48h subcultures on Sabouraud gentamicin chloramphenicol agar (Table 6).

Table 6) Antibiotics sensitivity of yeast species in cancer patients (n=25)

Yeast species	Strains
Candida albicans	8 (32.0%)
Candida glabrata	6 (24.0%)
Candida krusei	3 (12.0%)
Candida parapsilosis	2 (8.0%)
Candida tropicalis	2 (8.0%)
Candida kefyr	2 (8.0%)
Saccharomyces cerevisiae	2 (8.0%)
Total	25 (100%)

Discussion

Most cancer patients suffer from neutropenia due to chemotherapy [25]. Neutropenia occurs because of malignant tumors that infiltrate the bone marrow or due to some lymphomas or lymphocytic granulomatous leukemia, as well as due to immune causes, genetic and congenital or monoclonal pathogens of neutropenia in cancer patients [4].

The present study aimed to investigate some bacterial and fungal infections related to cancer patients who are undergoing chemotherapy and suffering from neutropenia.

According to the results of the present study, 30 blood samples from patients with leukemia had severe neutropenia depending on ANC and anti-neutrophil levels, and 8 samples from patients with breast cancer had moderate neutropenia, while the number of patients with moderate neutropenia caused by lung and bladder cancer was 4 (33.3%) and 2 (33.3%), respectively. The highest level of ANC and anti-neutrophil was found in breast cancer patients with 0.6×109/L and 9.6±0.3%, respectively.

Averin *et al.* [26] explained that half of the patients with metastatic cancer (48.6%) who received chemotherapy have high fibrous neutropenia, and breast cancer patients who received chemotherapy suffer from high fibril neutropenia risk levels (45.8%). Khalil [27] investigated 70 cases of diarrhea in 106 children with cancer, of which 50 cases were neutropenic, while 20 cases were not.

Few studies have been done on inflammatory molecules predicted to cause fever in neutropenic cancer patients, as these molecules have been estimated in the serum of patients and have the ability to cause fever in neutropenia patients and are associated with bacterial infection [28]. In our study, patients with bladder cancer had higher levels of IL-10, IL-8, and CCL2, followed by lung cancer patients, while lower levels of IL-10, IL-8, and CCL2 were observed in leukemia patients.

Buyukberber *et al.* [29] studied the soluble receptor levels of IL-2, IL-6, CXCL8 (C-X-C Motif Chemokine Ligand 8), CRP (C-Reactive Protein), IL-1b, and TNF-α (Tumor Necrosis Factor Alpha) in 22 patients with oncohematological diseases who had previously received chemotherapy, and at diverse moments after treatment, no cytokine was found to be prognostic of fever. Neutrophils are one of the basic immune defenses because they engulf, kill, and digest microorganisms, such as bacteria and fungi. Failure to perform this character leads to immunodeficiency, which leads to recurrent infections. Defects in the function of neutrophils may be quantitative or qualitative [30].

Gram-negative and drug-resistant bacteria cause multiple diseases in persons with neutropenia in addition to gram-positive bacteria [19]. This usually occurs due to several conditions, such as immunosuppression due to cancer or concomitant therapy, which leads to neutropenia and the breakdown of mucosal barriers. Placing a catheter on the blood vessels makes cancer patients more susceptible to bacteria. Chemotherapy and radiotherapy damage the oropharyngeal membrane, thus allowing Gram-negative organisms to enter the circulatory system or lung parenchyma more easily [30].

In the present study, 10 *E. coli* (16.7%) was observed in patients with leukemia and bladder cancer, 15 *Pseudomonas aeruginosa* (25.0%) in patients with breast cancer and leukemia, and 25 *Klebsiella pneumonia* (41.7%) in the patients with leukemia, breast cancer, and bladder cancer. However, samples from patients with lung cancer contained 4 coagulase-positive Staphylococci (6.7%) and 6 *Streptococcus pneumoniae* (10.0%), in addition to fungal infection.

Holland *et al.* [31] found that a wide variety of Gram-positive bacteria cause diseases in cancer patients with neutropenia, including Staphylococci, Streptococci, and Enterococci. The result of Shabaa [32] demonstrated that 45 (62.5%) α-hemolytic isolates are suspected to be pneumococci in cancer patients. Yadegarynia *et al.* [33] showed that the most detected microorganism was *Escherichia coli* (27.7%), followed by *Pseudomonas aeruginosa* (16%), *Acinetobacter baumannii* (10.5%), *Klebsiella pneumoniae* (8%), Coagulase positive Staphylococci (8%) and Coagulase negative Staphylococci (8%).

Broad-spectrum antibiotics are a suitable treatment for patients with febrile neutropenia. It contains the beginning of antimicrobial therapy in patients with neutropenia at the time of onset of fever. Protracted administration of antibiotics can lead to negative outcomes in immunocompromised patients [34].

Based on our Findings, in leukemia patients, two *E. coli* (6.7%) and two *P. aeruginosa* (6.7%) were sensitive to Amikacin, and three *E. coli* (10.0%) and two *P. aeruginosa* (6.7%) were sensitive to Piperacillin/Tazobactam, while *K. pneumonia* was resistant to all antibiotics. In breast cancer patients, two *P. aeruginosa* (25.0%) were sensitive to Levofloxacin, and two *K. pneumonia* (25.0%) were sensitive to Ciprofloxacin. One of the *E. coli* isolates (50.0%) from patients with bladder cancer showed sensitivity to both Cefixime and Ceftriaxone. In lung cancer patients, one of the *Staphylococcus aureus* (25.0%) were sensitive to Imipenem, Azithromycin, and Linezolid, and one of the *Streptococcus*

pneumonia (25.0%) were sensitive to both Ciprofloxacin and Levofloxacin.

In 2019, Al-Zubaidy *et al*. [35] reported that the most frequently effective antibiotic was Amikacin, followed by Imipenem for Gram-negative infections, and Ciprofloxacin, Tetracycline, and Aztreonam, followed by Chloramphenicol for Gram-positive organisms. Regarding Gram-negative organisms, the study of Al-Zubaidy *et al*. in 2020 [36] showed the highest sensitivity to Amikacin, Imipenem, and Piperacillin/Tazobactum.

It is also necessary to recognize neutropenic fever promptly and begin the use of extensive empirical antibiotics to evade sepsis and imaginable death [37].

Invasive Pulmonary Aspergillosis (IPA) is recognized as an increased infection in cancer patients with prolonged neutropenia and has a role in increased mortality of 50% or more [38]. Invasive Aspergillosis (IA) is a clinical problem in patients with neutropenia, and its finding is hard, so Galactomannan (GM) Enzyme-Linked Immunosorbent Assay (ELISA) is used to validate their implication in establishing IA [39]. The occurrence of IA is up to 22%, and the death rate is 60-70% when it happens during neutropenia. A robust diagnostic approach and quick antifungal treatment are important for survival in patients at risk for IA [40]. Neutropenia of more than 21 days increases the risk of invasive fungal infections among Bone Marrow Transplantation (BMT) recipients [41]. Also, specific disturbances in granulocyte function increase the risk of IA.

In the present study, a high level of GM-Ag was observed in neutropenic patients with lung cancer, and 25 strains of yeasts and yeast-like fungi, including 7 species, were identified, 23 of which belonged to the Candida genus.

Systemic candidiasis is a major complication of neutropenic cancer patients undergoing treatment. Most systemic fungal infections of the normal flora are caused by *Candida albicans*, which is more common among neutropenic patients [42]. The predisposing factors for systemic candidiasis in neutropenic patients with hematological malignancies differ according to the level of immune suppression and the role of the underlying neoplastic process [43, 44].

The digestive tract is the chief entry of Candida species in patients with acute neutropenia and leukemia and an area of endogenous microflora. Invasion of Candida to the bloodstream may happen through disturbance of the normal anatomical barriers.

Candida infections may be current as oropharyngeal candidiasis, esophagitis, candidemia, and acute or chronic disseminated candidiasis among this population [44].

Conclusion

Neutropenia is more common in leukemic patients. Gram-negative bacteria are the greatest public bacteria isolated in the patients under the study. *Klebsiella pneumonia* and *Streptococcus pneumonia* are the most common Gram-positive bacteria. All types of bacteria are resistant to most antibiotics.

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