



A Population-Based Study of Bacterial Spectrum in Febrile Neutropenic Patients

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ABSTRACT

Background: Because of great concerns about mortality and morbidity of infection in febrile neutropenic patients, the appropriate empirical antibiotic should be started immediately. Although there are established guidelines for the use of empirical therapy, local microbiological pattern and antibiotic susceptibility should be considered.

Objectives: The current study aimed to identify the etiological pathogens in febrile neutropenic cancer patients in Isfahan, Iran.

Patients and Methods: This single-centre population-based study was conducted on 81 febrile neutropenic patients referring to Sayed-Al-Shohada hospital, the only referral malignant care center in Isfahan, Iran. Demographic data, duration and kind of malignancy, duration from last chemotherapy, duration of fever, and also physical exam were recorded for each patient. Moreover, procalcitonin, CRP, ESR, white blood cells, hemoglobin, platelet, and absolute neutrophil count were measured. BACTEC and E-test were used for blood culturing and determining the antibiotic susceptibility.

Results: Out of 81 participants, 28.4% had positive blood cultures which mostly consisted of Gram-positive microorganisms. In addition, *Staphylococcus epidermidis* was the most isolated Gram positive bacteria (39.1%). ESR, CRP, and procalcitonin were significantly higher in patients with positive blood culture. The risk of infection increased with raise in duration of hospital stay, catheterization, increased pulse rate, increased oral temperature, low level of oxygen saturation, decreased systolic blood pressure, and low absolute neutrophile count. However, in this case, no relationship was found among the patients' age, diastolic blood pressure, respiratory rate, duration of diagnosis, duration from last chemotherapy, duration of fever, white blood cells, hemoglobin, platelet, and finally the type of malignancies.

Conclusions: It was concluded that Gram-positive bacteria were more prevalent as a cause of infection in the patients with malignancy and the most common pathogen was *S. epidermidis*. Larger studies are needed to determine the bacterial susceptibility of this center.

Keywords: Neutropenia; Epidemiology; Iran

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▶ Implication for health policy/practice/research/medical education:

While this study was the first of its kind conducted in Isfahan, its results could be used for better treatment and management of the patients of the center. Moreover, it can be a base for further studies with larger population to determine antibiotic sensitivity and resistance pattern.

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1. Background

Patients with malignancies are predisposed to severe infections, particularly during treatment with chemotherapeutic agents. One of the most common consequences of chemotherapy is neutropenia defined as the absolute neutrophil count (ANC) < 500 cell/ μL (1, 2). Also, secondary to chemotherapy, most cells of the human body undergo undesirable changes which cause disruptions of physical defense barriers such as skin and mucosa. Moreover, exposures to potentially pathogenic microorganisms increase because of the frequent use of foley and venous access catheters in these patients (1). These factors increase the risk of infection in cancerous patients.

Febrile neutropenia is defined as having oral temperature $\geq 38.3^\circ\text{C}$ or $\geq 38^\circ\text{C}$ for more than one hour when ANC is less than 500 cell/ μL or the reduction of ANC to 500 cell/ μL in the next 24 to 48 hours. It can be the first sign of bacterial infection which requires immediate consideration (1, 2). Also, reactions to drugs or blood products and tumor-associated fever can be the reason of fever. However, because of life-threatening nature of bacterial infection in neutropenic patients, immediate antibiotic therapy is crucial (3).

With the introduction of empirical, broad-spectrum antibiotics since about 30 years ago, the mortality and morbidity of such condition decreased significantly (4). Since then, algorithmic approach help more in managing these patients (5). Although the use of the combination of an anti-pseudomonal β -lactam and an aminoglycoside became a base for published guidelines in managing febrile neutropenia, such guidelines indicate that with the identification of causative pathogens, the antibiotic regimen can be changed. This strategy not only increases the efficacy of therapy, but also decreases the side effects and the cost. However, it is important to have a broad-spectrum coverage which prevents breakthrough bacteremia (6).

Since the causative bacteria are often anonymous, knowing the prevalence of them in these patients was essential to have an adequate antimicrobial therapy. In the 70's, in monomicrobial bacteremia, these bacteria mainly consisted of Gram-negative ones while with the advent of Coagulase-negative staphylococci (CoNS), Viridans streptococci, and Enterococci, this pattern changed to Gram-positive organisms in the 80's and 90's (7-9). In a comparison of febrile neutropenic children with adults, it was demonstrated that 64.2% and 57.9% of isolates were Gram positive in children and adults, respectively (10). However, today, febrile neutropenic populations with predominance of Gram-negative bacteria also exist.

In a single-center study in Israel, Gram-negative bacteria were predominant and their prevalence increased throughout two decades in adult population while in pediatric febrile neutropenic patients an increase in Gram-positive bacteria was shown. In two other studies conducted in Malaysia and Pakistan the same trend was

observed (2, 11). Dong-Gun Lee *et al.* (12) mentioned that as a general characteristic of Asia-Pacific region, Gram-negative microorganisms were the major pathogens of infection.

Differences in bacterial spectrum of different centers demonstrate the importance of knowing the etiological pathogens of each center for better management of febrile neutropenic patients. Additionally, with the growing incidence of antimicrobial resistance, knowledge about the pattern and antibiotic sensitivity of causative microorganisms of each region and center is vital. It should be mentioned that the type and severity of immunosuppression has a great effect on the interpretation of the results of laboratory diagnostic tests (13, 14).

2. Objectives

The current study aimed to evaluate the microbiological spectrum and susceptibility patterns of pathogens in febrile neutropenic patients over one year in a university hospital of Iran.

3. Patients and Methods

3.1. Setting

This single-center population-based study was conducted in the only referral university cancer hospital of Isfahan (Iran) from February 2010 to February 2012.

3.2. Patient Eligibility

Febrile neutropenia was defined as oral temperature $\geq 38.3^\circ\text{C}$ or $\geq 38^\circ\text{C}$ for more than one hour when ANC was less than 500 cell/ μL or the reduction of ANC to 500 cell/ μL in the following 24 to 48 hours. The patients were randomly selected among the Sayed-Al-Shohada hospital patients, a referral hospital for patients with malignancies. Febrile neutropenic patients who were above 14 years and had not received empirical antibiotic therapy more than 12 hours of their commencements in the study were included.

A total of 81 febrile neutropenic patients were enrolled. All the steps and procedures were explained to the participants and written informed consents were taken from them. This trial was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Isfahan University of Medical Sciences Ethics Committee.

3.3. Clinical and Laboratory Evaluations

Subjects were interviewed by a physician and data including age, gender, underlying malignancy, diagnosis date, duration of current hospital stay, duration of fever before sending blood culture, duration of having urinary or venous catheter were collected.

A phlebotomist was trained to do the venipuncture and obtain blood cultures in a manner to avoid any contamination during the procedure. Blood samples were taken

for hemoglobin, white blood cell count, platelet count, Absolute neutrophil count(ANC), C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), and procalcitonin (PCT) analyses. ESR was determined by Westergren method while serum CRP was measured by immunoturbidimetric method (COBAS Integra C reactive protein (Latex) test, Roche Diagnostics, Basel, Switzerland). Also, PCT levels in serum samples were determined using enzyme-linked immunoassay (ELISA kit: VIDAS BRAHMS Procalcitonin, bioMérieux, Lyon, France). All tests were performed according to manufacturer's instructions and recommendations.

3.4. Bacterial Isolates

For blood cultures, the BACTEC 9050 blood culture instruments (Bectone Dickinson, Baltimore, Md.,USA) was used. The identification of etiological pathogens was based on routine bacteriological procedures. Routinely, the bottles were incubated in BACTEC for seven days. During these days, if the system alerted for positive blood culture, 3 to 5 drops of blood culture samples were inoculated on blood and chocolates agar plus 5% sheep blood. Then, after 24h of incubation aerobically, the samples were stained by Gram's method.

3.5. Susceptibility Testing

The E-test from AB Biodisk, (Solna, Sweden) was employed in this study. The choice of antibiotic for each pathogen and the Minimum Inhibitory Concentration (MIC) were based on Clinical and Laboratory Standards Institute (CLSI) guidelines. For most of the isolates PDM Antibiotic Sensitivity Medium II (AB Biodisk) was used while 5% horse blood was added to medium for streptococcal isolates. The Fastidious Anaerobe Agar (IDG, UK) was used for anaerobic bacteria and Mueller-Hinton agar II (Difco Laboratories, Detroit, USA) plus 4% NaCl was employed to determine the susceptibility of the staphylococcal isolates to oxacillin.

3.6. Statistical Analysis

SPSS software version 15 (SPSS® Inc.) was employed to analyze the data, using Chi Square test and independent sample t-test to evaluate the relationship between bacterial infection vs. qualitative and quantitative variables, respectively. Z was considered as 0.95 while the P value of < 0.05 was defined significant for all testes.

4. Results

4.1. Study Population

Out of 81 participants, 23 (28.4%) of them had positive blood culture while 58 (71.6%) patients had isolated febrile episodes. 30 women and 51 men participated in this study which 20.0% and 33.3% of them had positive blood culture, respectively. No significant difference was indicated in

this respect (P value = 0.1).

4.2. Clinical and Laboratory Evaluations

Table 1 demonstrates the frequency (percentage) of different underlying malignancies based on the result of patients' blood culture. No significant differences were found between the bacterial infection and the underlying malignancy (P value > 0.05).

The characteristics of 81 febrile neutropenic patients based on the results of their blood culture are summarized in Table 2.

The percentage of graded scale of CRP level were as follows: in negative blood culture group 31.03%, 32.75%, 22.41%, 13.79%, and 0% of them had 0, +1, +2, +3, and +4 level of serum CRP respectively, while in the same order, it was 0%, 0%, 26.08%, 56.52%, and 17.39% for positive blood culture group. The Mann-Whitney analysis demonstrated a significant difference between the level of CRP and positive blood culture (P value = 0.00).

4.3. Microorganisms and Susceptibility to Antimicrobial Agents

A total of 23 microorganisms were isolated which 56.4% (13) of them were Gram-positive bacteria, 17.4% (4) were Gram-negative *bacillus*, 3% (2) was *Fusobacterium necrophorum* (anaerobic bacilli), 4.3% (2) was *Mycoplasma pneumonia* (atypical bacteria), and 17.4% (4) were fungi. The most frequently isolated bacteria were *S. epidermis* with 39.1% (7). Other Gram-positive bacteria were consisted of *S. aureus* with 4.3% (2), *streptococcus viridians* with 4.3% (2), and *S. pneumonia* with 7.8% (1). Gram-negative *bacillus* included two *Pseudomonas aeruginosa* and two *Escherichia coli*, while one of the fungi was *Mucor Spp.*, one was *Candida albicans*, and two were *Aspergillus fumigates*. The antibiotic sensitivity and resistance pattern of the isolated bacteria is given in Table 3.

Table 1. The Frequency (Percentage) of Underlying Malignancies Based on the Result of Patients' Blood Culture.

	Positive, No. (%)	Negative, No. (%)	Total, No.	P value
AML	6 (27.3)	16 (72.7)	22	$P > 0.05$
ALL	11 (44.0)	14 (56.0)	25	$P > 0.05$
CML	1 (25.0)	3 (75.0)	4	$P > 0.05$
CLL	0 (0)	3 (100)	3	$P > 0.05$
HCL	1 (50.0)	1 (50.0)	2	$P > 0.05$
Breast cancer	1 (20.0)	4 (80.0)	5	$P > 0.05$
Ovarian cancer	0 (0)	2 (100)	2	$P > 0.05$
Lymphoma	1 (16.7)	5 (83.3)	6	$P > 0.05$
MM	1 (16.7)	5 (83.3)	6	$P > 0.05$
Unknown	0 (0)	4 (100)	4	$P > 0.05$
Total	22	57	79	$P > 0.05$

Table 2. Comparison of Characteristics of 81 Febrile Neutropenic Patients Based on the Result of Their Blood Culture.

	Positive Blood Culture, Mean ± SD	Negative Blood Culture, Mean ± SD	P value
Age, y	43.3 ± 18.7	48.2 ± 17.2	0.25
SBP	111.5 ± 14.9	120.6 ± 18.5	0.03
DBP	71.3 ± 9.7	76.8 ± 15.0	0.10
PR	88.8 ± 12.4	84.4 ± 7.2	0.05
RR	21.1 ± 3.0	19.4 ± 4.1	0.07
Oral T	39.0 ± 0.5	38.7 ± 0.5	0.02
O2 Sat	87.6 ± 8.7	92.0 ± 3.6	0.00
Duration of diagnosis, mo	11.7 ± 20.6	17.6 ± 31.1	0.43
Duration from last chemotherapy, day	23.3 ± 33.6	27.8 ± 22.2	0.57
Duration of catheterization, day	25.9 ± 26.7	6.1 ± 7.3	0.00
Duration of fever, hour	39.3 ± 43.1	23.3 ± 24.2	0.49
Duration of hospital stay, day	14.1 ± 8.4	4.8 ± 5.5	0.00
WBC ×10 ³	2161.0 ± 6971.0	3782.4 ± 5685.7	0.28
HB	8.5 ± 1.7	9.1 ± 1.5	0.11
PLT ×10 ³	31826.1 ± 27996.1	60874.1 ± 83156.1	0.10
ANC ×10 ³	190.2 ± 230.6	367.4 ± 293.7	0.01
PCT	29.9 ± 14.1	2.9 ± 5.0	0.00
ESR	75.0 ± 24.0	49.2 ± 23.1	0.00

5. Discussion

During the past decades, the microbiological pattern of infection in febrile neutropenic patients with malignancies has considerably changed. This change includes a shifting epidemiology from Gram-negative to Gram-positive microorganisms. Nowadays, the most common bacteria in these patients are Coagulase-negative staphylococci, Alpha-haemolytic streptococci, *S. aureus* (9, 15, 16). Moreover, because of great concerns about mortality and morbidity of infection in such patients, antibiotic therapy should be initiated as soon as possible. This situation seems challenging since the bacteriological tests take at least 3-4 days. Therefore, the knowledge of prevalent pathogens in each region is a crucial key to begin the appropriate empirical antibiotic therapy immediately (17).

The blood cultures of the patients under study mostly consisted of Gram-positive microorganisms while Gram-negative bacteria and fungi stood in second place simultaneously. Moreover, *S. epidermidis* was the most common isolated bacteria. In the 70`s, Gram-negative pathogens were responsible for 70% of blood stream infections while in mid-80`s Gram-positive ones began to predominate and in the late 90`s, these pathogens account for nearly 70% of bacteremia (9, 10, 18-20).

In a study conducted from 1986 to 1993 in a single institution in Spain, a continuous rise in Gram-positive bacteremia was seen, although the incidence of Gram-negative bacteremia remained unchanged. Staphylococci

and *S. viridans* were the most commonly isolated bacteria in this study (21). Moreover, in a multicentre study on febrile neutropenic patients in the USA Wisplinghoff *et al.* (19) reported the outweigh of Gram-positive microorganisms as a cause of 62% and 76% of blood stream infections in 1995 and 2000 respectively, while only 22% and 14% of all blood stream infections originated from Gram-negative ones at the same time (19).

Another report from a New Zealand hospital also showed the predominance of Gram-positive bacteria. In the current study, Gram-positive cocci accounted for 46% of isolates while only 35% of which were Gram-negative bacilli (6). Additionally, Castagnola *et al.* (22) reported that in their study 57% and 41% of bacteremia in febrile chemotherapy-induced neutropenia were caused by Gram-positive and negative organisms respectively while in a study in Belgium, the relative frequencies of Gram-positive, Gram-negative, and polymicrobial bacteremia in the same patients were 57%, 34%, and 10%, respectively (23).

This changing pattern has been explained by some factors. As one of the important factors, intensive courses of chemotherapy cause oro-intestinal mucosa damage predisposing the patients to infection with Gram-positive microorganisms. Also, it was claimed that during chemotherapy the use of prophylactic oral antibiotics like selective intestine decontamination results in diminution of intestinal Gram-negative flora. Another factor is the frequent use of central venous

catheters which contribute to developing skin-derived Gram-positive infections (1). Hand washing, better isolation and generally better sanitation of patients in oncology wards were other reasons of this event (17). In addition, as one of the main reasons, the use of some antibiotic prophylaxis such as third-generation cephalosporins and fluoroquinolones which are more active

against Gram negative bacteria may explain this trend of changing (24). However, not only there are populations with predominance of Gram-negative organisms such as developing countries, but also it is claimed that the reemergence of Gram-negative bacteria as a major cause of infection in such patients were seen very recently (25).

Table 3. Sensitivity and resistance pattern of common used antibiotics against isolated pathogens

	Staphylococcus	epidermidis	Staphylococcus aureus	Streptococcus viridians	Streptococcus Pneumonia	Gram negative bacilli	Fusobacterium necrophorum Mycoplasma pneumonia
Penicillin, No. (%)							
S	3/9 (33.3)	0/1 (0)	0/1 (0)	0/2 (0)	-	0/1 (0)	-
R	6/9 (66.6)	1/1 (100)	0/1 (0)	2/2 (100)	-	0/1 (0)	-
Oxacillin, No. (%)							
S	5/9 (55.5)	0/1 (0)	-	-	-	-	-
R	3/9 (33.3)	1/1 (100)	0/1 (0)	-	-	-	-
Ceftazidim, No. (%)							
S	5/9 (55.5)	0/1 (0)	0/1 (0)	1/2 (50)	1/4 (25.0)	-	-
R	3/9 (33.3)	1/1 (100)	0/1 (0)	1/2 (50)	3/4 (75.0)	-	-
Cefepime, No. (%)							
S	6/9 (66.6)	0/1 (0)	1/1 (100)	2/2 (100)	3/4 (75.0)	-	-
R	2/9 (22.2)	1/1 (100)	0/1 (0)	0/2 (0)	0/4 (0)	-	-
Meropenem, No. (%)							
S	8/9 (88.8)	0/1 (0)	1/1 (100)	2/2 (100)	4/4 (100)	1/1 (100)	-
R	0/9 (0)	1/1 (100)	0/1 (0)	0/2 (0)	0/4 (0)	0/1 (0)	-
Imipenem, No. (%)							
S	8/9 (88.8)	0/1 (0)	1/1 (100)	2/2 (100)	4/4 (100)	1/1 (100)	-
R	0/9 (0)	1/1 (100)	0/1 (0)	0/2 (0)	0/4 (0)	0/1 (0)	-
Piperacillin tazobactam, No. (%)							
S	7/9 (77.7)	0/1 (0)	1/1 (100)	-	3/4 (75.0)	1/1 (100)	-
R	2/9 (22.2)	1/1 (100)	0/1 (0)	-	1/4 (25)	0/1 (0)	-
Vancomycin, No. (%)							
S	9/9 (100)	1/1 (100)	1/1 (100)	2/2 (100)	-	-	-
R	0/9 (0)	0/1 (0)	0/1 (0)	0/2 (0)	-	-	-
Ciprofloxacin, No. (%)							
S	7/9 (77.7)	0/1 (0)	0/1 (0)	0/2 (0)	2/4 (50.0)	-	1/1 (100)
R	1/9 (11.1)	1/1 (100)	1/1 (100)	0/2 (0)	0/4 (0)	-	0/1 (0)
Azithromycine, No. (%)							
S	-	-	-	0/2 (0)	-	-	1/1 (100)
R	-	-	-	2/2 (100)	-	-	0/1 (0)
Metronidazole, No. (%)							
S	-	-	-	-	-	1/1 (100)	-
R	-	-	-	-	-	0/1 (0)	-

Abbreviations: S, Sensitive; R, Resistance

During a study period of 14 years from 1988–2001 in Sweden, no epidemiological shift from Gram-negative to positive-organisms was seen in patients with malignant blood disorders and the balance between these two kinds of microorganisms was unchanged over the study period. In addition, Coagulase negative staphylococci with 17% was the predominant isolated bacteria and *E. coli* with 16% stood in second place (26). Moreover, Cattaneo *et al.* (27) stated that their study was an evidence for an epidemiological shift from Gram-positive to negative-bacteria in patients with hematological malignancies while *E. coli* was the most frequent organism. Also, there are other reports of emergence of Gram-negative bacteria mainly consisted of *P. aeruginosa* and Enterobacteriaceae which stands for nearly 50% of all documented infections (23).

Moreover, while the current study results demonstrated that 28.4% of the febrile neutropenic patients had positive blood culture, only 2.6% of blood cultures of such patients were positive in the previous retrospective study in the same center (28). Such difference can be explained by the use of BACTEC blood culture system instead of conventional culture method in the present study. In this center because of the higher cost of BACTEC, the conventional culture method is used for routine bacteria isolation. As indicated, the BACTEC system was much more efficient to isolate bacteria especially in shorter time and also had a lower incidence of contamination compared with the other systems (29, 30).

Finally, the current study results showed that the presence of fever in neutropenic patients did not actually mean the infection. Therefore, risk assessment for infection in these patients is a crucial point which should be considered for prescription of empirical antibiotic. ESR, CRP, and procalcitonin were markers of infection in the febrile neutropenic patients under study. In addition, the risk of infection increased with raise in duration of hospital stay, catheterization, increased pulse rate, increased oral temperature, low level of oxygen saturation, decreased systolic blood pressure, and low absolute neutrophil count. However, in this case, no relationship was found with the patients' age, diastolic blood pressure, respiratory rate, duration of diagnosis, duration from last chemotherapy, duration of fever, white blood cells, hemoglobin, platelet, and finally the type of malignancies.

This cross-sectional study on febrile neutropenic patients with malignancy was the first of its kind conducted in Isfahan, Iran. However, the small study population was the drawback of this study which resulted in limitation for interpretation of some results. Therefore, larger studies are needed to determine the pattern of antibiotic sensitivity and resistance of these pathogens.

It was concluded that Gram positive-bacteria were more prevalent as a cause of infection in the patients with malignancy and the most common pathogen was *S. epider-*

midis. Larger studies are required to confirm these results and to determine antibiotic sensitivity and resistance patterns.

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Authors' Contribution

None declared.

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