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Frequency of bloodstream infection in febrile neutropenic patients, experience from a developing country

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ABSTRACT

Introduction: About 20% of febrile neutropenic patients are presented with bloodstream infection which is a leading cause of mortality among these patients. Awareness of the locally prevalent pathogens and their susceptibility pattern is important for proper treatment of infection which improves survival in these patients. The objective of this study was to determine the frequency of bloodstream infection in patients with febrile neutropenia admitted in Abbasi Shaheed Hospital.

Methods: This cross-sectional study was conducted in the Medical wards in Abbasi Shaheed Hospital, Karachi from 21-2-2016 to 20-8-2017. Patients of over 15 years of age of either gender with severe neutropenia were included in this study. Patients with noninfectious cause of fever, or fever prior to neutropenia were excluded. Patients meeting inclusion criteria were enrolled after taking informed consent. About 2–5 ml blood was collected under aseptic measures in Bactac culture bottles. Blood samples were sent to lab within 30 min of collection. Antimicrobial sensitivity testing of all isolates was performed on diagnostic Sensitivity test plates by Kerby – Bauer Method. Patients were referred back to treating physician if blood culture is positive. The data was analyzed using SPSS version 20.

Results: Of 200 patients, the mean age was 25.8 ± 5.7 years, 120 (60%) were male with male to female ratio of 1.5:1, 89 (44.5%) had low grade fever (Temp. ≤102 °C) and 111 (55.5%) had high grade fever(Temp. > 102 °C). The frequency of *staphylococcus aureus* was 16%, *E. coli* was 14.5%, *Pseudomonas* 8.5% and *Klebsiella* 15.5%

Conclusions: It is concluded that the frequency of *staphylococcus aureus* was 16%, *E. coli* was 14.5%, *Pseudomonas* 8.5% and *Klebsiella* 15.5%

1. Introduction

Patients with febrile neutropeniaare more susceptible to life threatening bacterial infections due to lack of inflammatory response [1]. Hence, febrile neutropenia should be dealt as an emergency and administration of empirical antibiotics may improve survival in these patients [2].According to American college of physicians and society of critical care medicine which include axillary temperature > 38C, heart rate > 90/mainland respiratory rate > 20/min. Absolute neutrophic count is 500/mm^3 The reported risk of bloodstream infection in patients with febrile neutropenia is between 11 and 38% [3].

Staphylococcus aureus was the most common isolate among the Gram-positive organisms (53%), while *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* were the 3 leading Gram-negative isolates (42%) [4].Mortality rate due to gram-negative pathogens was 18% and gram-positive pathogen was 5% [5,6].

Compared to previous reports, the pattern of bacterial isolates and their resistance to antibiotics has changed over the past years. Gram-positive organisms predominated in the 50s and 60s, gram negative later, the emergence of multi-drug resistant aerobic rods in 90s and a shift back to gram positive in last two decades in some regions has created problems of effective therapy [7,8].

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Management of patients with febrile neutropenic is complex and involves careful consideration of multiple factorslike primary underlying etiology, duration, and severity of the neutropenia, Improved broad-spectrum antibiotic agents, combined with improved supportive care, have improved the prognosis for most patients with severe neutropenia. A study showed more than 30 years ago that there was an inverse relationship between the absolute neutrophil count and life threatening infections [9,10].A delay of more than 48 h in the administration of appropriate antibiotics may result in a mortality rate of approximately 50% [10].

Identification of the locally prevalent pathogens and their susceptibility pattern is important, before putting neutropenic patients on empiric antimicrobial regimens, Bacterial infections are the major cause of morbidity and mortality among neutropenic patients. Thus, the objective of the study was to determine the frequency of bloodstream infection responsible for blood stream infection (BSI) in febrile neutropenic patients admitted in xxxxxx Hospital so that appropriate antibiotic therapy should be started to reduce mortality.

2. Material and methods

This cross sectional study was conducted in Department of Medicine, xxxxxxxx Hospital from 21-February-2016 to 20-August-2017. Department of Medicine is a 120 bedded medical unit admitting approximately X patients per day.

Patients of age over 15 years with moderate to severe neutropenia due to infection (viral, bacterial, protozoal and fungal) or immune neutropanias or hypersplenism or hematological and non-hematological malignancies or vitamin B12, folate deficiency or radiation or chemotherapy or hemodialysis were included in this study. Patients of age < 15 years developing fever due to noninfectious causes as after 6–24 h of transfusion of blood products or drug infusion or had fever prior to neutropenia or those who did not give written consent were excluded from the study. Patients from medical unit were selected after the approval of the ethical board review committee of hospital and College of Physicians and Surgeons. Patients who fulfilled inclusion criteria were enrolled in the study after taking informed consent. The data were collected from all neutropenic patients (defined as, an absolute neutrophil count (ANC) of less than 1500/ml and running fever).Fever was defined as a single oral temperature ≥38.3 °C (101 °F) for atleast 1 h or a temperature of ≥38 °C or 100.4 °F on two or more occasions within 12-24-hourperiod. Four to five ml of venous blood was taken under aseptic technique and is collected in a Bactec blood cultures bottle. Blood culture was sent to laboratory within 20 min of collection. Antimicrobial sensitivity testing of all isolates was performed on diagnostic sensitivity test plates by Kerby – Bauer Method; *Staphylococcus aureus* was identified as round grape like colonies under microscopy; *Pseudomonas aeruginosa*, as rod shaped bacteria with unipolar motility; *E. coli*, as rod shaped, 2 mm long and 0.5 μm in diameter and *Klebsiella pneumonae* was identified as small rod shaped structures inoculated in MacConkey culture. Data were recorded in a structured questionnaire. Patients were referred back to treating physician if blood culture is positive for further assessment and treatment.

The sample size of 200 was calculated assuming prevalence of neutropenia of 7.2%, bond on error of estimation of 4% and confidence level of 95%. Data analysis was performed through SPSS Version-20. Mean and SD was calculated for age, and temperature. Frequency and percentages was calculated for various bacterial agents which were *staphylococcus aureus*, *E.coli*, *Pseudomonas aeruginosa*and *Klebsiella pneumonae*. Stratification was done based on age and gender to see effect on outcome variable through Chi-square test and p-value of < 0.05 was considered significant.

3. Results

A total of 200 patients were enrolled in this study. Mean age was 25.8 ± 5.7 years, 120 (60%) were male with male to female ratio of 1.5:1, 89 (44.5%) had low grade fever (Temp. 102 C) and 111 (55.5%) had high grade fever.The frequency of *Staphylococcus aureus* was 16%, *E. coli* was 14.5%, *Pseudomonas aeruginosa* 8.5% and *Klebsiella pneumonae was* 15.5% (Table 1) (see Table 2 and Table 3).

Table 1
Characteristics of patients.

Age	
Mean ± SD	25.8 ± 5.7 years
Sex	
Male	80 (40%)
Female	120 (60%)
Temperature	
Low grade (102 F)	89 (44.5%)
High grade (> 102 F)	111 (55.5%)
Pathogens	
Staphylococcus aureus	32 (16%)
E. coli	29 (14.5%)
Pseudomonas aeruginosa	17 (8.5%)
Klebsiella pneumonae	31 (15.5%)

Stratified analysis showed: Mean age of *Staphylococcus aureus* positive cases was 25.2 ± 4.7 years compared to 25.9 ± 5.8 years in *Staphylococcus aureus*cases (p-0.49) and among male patients 19.2% had *Staphylococcus aureus*cases compared to 11.3% in female cases (p-0.16); mean age of *E. coli* positive cases was 28.2 ± 6.1 years compared to 25.5 ± 5.5 years in *E. coli* negative cases (p-0.02) and among male patients 14.2% had *E. coli* positive cases compared to 15% in female cases (p-0.51); Mean age of *Pseudomonas aeruginosa* positive cases was 25.6 ± 3.6 years compared to 25.8 ± 5.8 years in *Pseudomonas aeruginosa*negative cases (p-0.82) and among male patients 7.5% had *Pseudomonas aeruginosa* positive cases compared to 10% in female cases (p-0.35) and mean age of *Klebsiella pneumonae* positive cases was 25.9 ± 4.6 years compared to 25.8 ± 5.8 years in *Klebsiella pneumonae* negative cases (p-0.93) and among male patients 14.2% had *Klebsiella pneumonae* positive cases compared to 17.5% in female cases (p-0.32).

4. Discussion

Febrile neutropenia is the development of fever, often with other signs of infection, in a patient with neutropenia, an abnormally low number of neutrophil granulocytes (a type of white blood cell) in the blood. The term neutropenic sepsis is also applied, although it tends to

Table 2
Stratified analysis of pathogens by age.

	STAPHYLOCOCCUS AUREUS		P-value
	Positive	Negative	
Mean age	25.2 ± 4.7	25.9 ± 5.8	**0.49**
	PSEUDOMONAS AERUGINOSA		P-value
	Positive	Negative	
Mean age	25.6 ± 3.6	25.8 ± 5.8	**0.82**
	E. COLI		P-value
	Positive	Negative	
Mean age	28.2 ± 6.1	25.5 ± 5.5	**0.02**
	KLEBSIELLA PNEUMONAE		P-value
	Positive	Negative	
Mean age	25.9 ± 4.6	25.8 ± 5.8	**0.93**

Table 3
Stratified analysis of pathogens by sex.

Pathogens	Sex		p-value
	Male	Female	
Staphylococcus aureus	23 (19.2%)	9 (11.3%)	0.16
Pseudomonas aeruginosa	9 (75%)	8 (10%)	0.35
E.coli	17 (14.2%)	12 (15%)	0.51
Klebsiella pneumonae	17 (14.2%)	14 (17.5%)	0.32

be reserved for patients who are less well. Fever is actually caused by infection in 50% of cases, and bloodstream infection (bacteria in the bloodstream) may be present in as many as 20% of all patients with an absolute neutrophil count under [10.12].

Febrile neutropenia can develop in any form of neutropenia, but is most generally recognized as a complication of chemotherapy when it is myelosuppressive (suppresses the bone marrow from producing blood cells). Generally, patients with febrile neutropenia are treated with empirical antibiotics until the neutrophil count has recovered and the fever has abated; if the neutrophil count does not improve, treatment may need to continue for two weeks or occasionally more [11].

Bacterial infections in neutropenic patients are a major cause of morbidity and mortality [13,14]. Knowledge of the locally prevalent pathogens and their susceptibility patterns is important before putting these patients on empiric antimicrobial therapy. Thirty years ago most of the infections in these patients were caused by aerobic Gram-negative bacilli. Over the last twenty years however, a shift in the bacterial spectrum towards Gram-positive cocci has been reported in the West [14–17].Although the exact cause of this shift is not known, long-dwelling intravascular devices, fluoroquinolone prophylaxis and chemotherapy-induced mucositis have been implicated [18,19]. This trend however has not been prominent in the developing world [20].

Coagulase negative staphylococcus (CoNS) are the commonest organisms isolated in the Western countries followed by *Staphylococcus aureus*. Other Gram-positive cocci like enterococci and viridans streptococci are increasingly being reported as important causes of infection. Among the Gram-negative bacteria, *Escherichia coli*, *Pseudomonas aeruginosa* and Klebsiella sp. are the common pathogens [21–23]. In a study although Gram-negative bacilli (57%) were the predominant isolates, statistically their isolation rate did not significantly differ from Gram-positive isolates ($0.5 > p > 0.1$). Almost half (43%) of the patients were infected with Gram-positive cocci, CoNS being the commonest (26%). In 1998, Karamatet al [24] had reported a predominance of Gram-negative isolates from neutropenic patients in the same setting. Among Gram-positive organisms, *Staphylococcus aureus* was the commonest isolate in their study [13].A definite shift towards Gram-positive microorganisms has been observed in our study with CoNS as the predominant isolates.

In this study the frequency of staphylococcus aureus was 16%, e. coli was 14.5%, Pseudomonas 8.5% and Klebsiella 15.5% in febrile neutropenic patients. In a study was aiming to study trends in bacterial spectrum reported that the most common organisms were: *Escherichia coli* (23.1%), Staphylococcus epidermidis (13.9%), *Pseudomonas aeruginosa* (12.5%) and *Staphylococcus aureus* (7.9%). In another study, it was reported that gram-positive infections accounted for 49% (with coagulase-negative staphylococci the most frequent); monomicrobial, gram-negative infections accounted for 36% (with *Escherichia coli* the most frequent); and 15% of infections were polymicrobial. The findings of two study showed that organism varies in different population.

5. Conclusion

It was concluded from this study that the frequency of bloodstream infection in patients of febrile neutropenia was *Staphylococcus aureus* 16%, *E. coli* was 14.5% *Pseudomonas* 8.5% and *Klebsiella* 15.5%.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

Yes, ethical review committee approved this study.

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None.

Author contribution

Dr. Hafiz Abdul Basit Siddiqui, has made contributions to conception and design, interpretation of data, drafting the manuscript and revising it critically for important intellectual content. Dr. Rabeea Azmat has made contribution to acquisition and interpretation of data and drafting the manuscript. Dr. Shiyam Sundar Tikmani has made contribution in acquision and interpretation of data and drafting the manuscript. Dr. Shumaila Rafi has made contribution to acquisition and interpretation of data and drafting the manuscript. Dr. Beenish Syed has made contribution to acquisition and interpretation of data. Hareem Rehman has made contribution in data collection and drafting the manuscript. Dr. Tahir Rizwan Khan has made interpretation of data and in revising the manuscript. Dr. Saleemullah Paracha has made contribution in revising the manuscript.

Conflicts of interest

None.

Trial registry number

Not applicable to this study.

Guarantor

Hafiz Abdul Basit Siddiqui.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2018.09.004.

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