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Epidemiology and source of infection in patients with febrile neutropenia: A ten-year longitudinal study

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ABSTRACT

Objectives: No recent studies are available from Saudi Arabia on the etiology of febrile neutropenia. The objective of this study was to describe the characteristics of patients with febrile neutropenia and to calculate the rate of occurrence of bacteremia in these patients.
Methods: This is a hospital-based study of patients admitted with febrile neutropenia from 2006 to 2015.
Results: A total of 372 distinct episodes of febrile neutropenia representing 231 patients were included. Hematologic malignancies constituted 56.6% of the episodes. Positive blood cultures were reported in 13.5% with equal frequency of Gram-negative bacilli and gram positive cocci. The most commonly suspected sites of infection were blood 10.8% and pulmonary 9.2%, and the majority (72.5%) was thought to have no identifiable source of infection. Of all the episode, 32% had central venous catheters. The most frequently used single antimicrobial agents were imipenem (38%) and ceftazidime (7.5%). The mortality rate was 11.2% and it was significantly associated with the presence of bacteremia 24.4% versus 12.4% ($P = 0.016$). Mortality was not significantly association with age, type of malignancy, presence of central venous catheter, or the severity of neutropenia. Compared to patients with hematological malignancy, patients with solid organ malignancy were more likely to be female 62% versus 14.9% ($P < 0.001$) and were less likely to have bacteremia 8.7% versus 17.1%, $P = 0.042$, respectively.
Conclusion: We had shown that febrile neutropenia in this study has a low rate of bacteremia and that about 45% received the recommended initial empiric therapy.

Introduction

The occurrence of febrile neutropenia is a major cause of morbidity and mortality in patients with hematologic and solid organ malignancy. It is estimated that 10–50% of solid tumor patients and 80% of hematologic malignancies will develop fever during chemotherapy-induced neutropenia [1–3]. Febrile neutropenia occurs at a rate of 7.83 cases/1000 cancer patients and 43.3 cases/1000 patients with hematological malignancy [4]. There are sparse data regarding this entity from the Middle East in general and Saudi Arabia in specific [5,6] and the data are limited to childhood neutropenia [7] or specific population such as breast cancer [8]. Data on the epidemiology and compliance with recommendations for empiric antimicrobial agents are needed. In one study from Saudi Arabia, the compliance rate was 45% among 100 patients with febrile neutropenia [7]. Thus, we examine the occurrence, the epidemiology and clinical outcome of febrile neutropenia in one hospital in Saudi Arabia over a 10 year period.

Materials and methods

We included all hospitalized patients who met the case definition of febrile neutropenia. The definition followed the Infectious Diseases Society of America (IDSA) definition of the occurrence of fever of a single oral temperature of >38.3 °C (101 °F) or a temperature of >38 °C (100.4 °F) sustained over a 1-h period in a patient

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Table 1
Summary of the characteristics and source of infection in the included febrile neutropenia cases.

	Number	%
Male: female ratio	1.16 (ratio)	–
Hematologic malignancy	210	56.6
Positive blood culture	50	13.5
Candida	1	0.3
GNB	20	5.4
GPB	5	1.3
GPC	19	5.1
Multiple	5	1.3
Presence of CVC	118	31.8
Likely source of infection		
Blood	40	10.8
Bone	1	0.3
GI	7	1.9
Lung	34	9.2
No identifiable source	269	72.5
SSTI	6	1.6
Urine	14	3.8
Positive urine culture	13	3.5
Radiographic evidence of pneumonia on CXR	300	80.9
Mortality	41	11.1

GNB: Gram negative bacilli; GPB: Gram Positive Bacilli; GPC: Gram positive cocci; GI: gastrointestinal tract; SSTI: Skin and soft tissue infection; CVC: central venous catheter; CXR: Chest X-ray

with absolute neutrophil count (ANC) of <500 cells/mm^3 or an ANC expected to decrease to <500 cells/mm^3 in the following 48 h [1,2]. The study was conducted between 2006 and 2015. The hospital is a 350-bed general hospital and provides medical care for approximately 370,000 individuals eligible for medical care. There are 5 intensive care units (cardiac, medical, surgical, pediatric, and neonatal) and an active hematology/oncology service [9].

A standardized Microsoft Excel data collection sheet was used to collect data from the paper chart and electronic medical record. The following parameters were collected: demographics, clinical, radiographic and microbiologic data. The study was approved by the Johns Hopkins Aramco Healthcare Institutional Review Board (IRB).

Statistical analysis was done using Minitab® (Minitab Inc. Version 17, PA16801, USA; 2017). We calculated the mean age and length of stay (±SD) of patients. Descriptive analyses were done for demographic, clinical and laboratory data. Bivariate analysis was done to compare those who had solid organ or hematologic malignancy comparison between those who died and those who survived and for those with neutropenia (ANC 100-500) and those with profound neutropenia (ANC < 100). For categorical variables, we used Chi-square test and the independent samples t-test for continuous variables. We also attempted a multivariate analysis using a backward strategy. A P-value of less than 0.05 was considered to indicate statistical significance.

Results

A total of 372 distinct episodes of febrile neutropenia representing 231 patients were included (Table 1). Hematologic malignancies constituted 56.6% of the episodes. Of all the episode, 32% had central venous catheters. Positive blood cultures were reported in 13.5% with equal frequency of Gram-negative bacilli (5.4%) and gram positive cocci (5.1%). Candidemia was found in 0.3% of all episodes. The most commonly suspected sites of infection were: blood 10.8% and pulmonary 9.2%, and the majority (72.5%) was thought to have no identifiable source of infection. In patients who had a chest radiograph, it was thought to show an infection in 81%. The mortality was 11.2%. The most frequently used single antimicrobial agents were imipenem (38%) and ceftazidime (7.5%), and other patients received variable combination therapy.

Table 2
A comparison of patients who survived and those who died in febrile neutropenia patients.

	Survived number (%)	Deceased number (%)	P value
Number	331	41	
Mean age	45.8 + 22.3	49 + 24.4	0.23
Hematologic	184 (55.6)	26 (63.4)	0.42
CVC	111 (33.5)	7 (17)	0.34
Bacteremia	41 (12.4)	10 (24.4)	0.016
CXR with infection	263 (79.5)	37 (90)	0.23
Urine positive	35 (13.5)	4 (4)	0.017
Severe neutropenia	136 (41.2)	12 (29.3)	0.14

CVC: central venous catheter; CXR: Chest X-ray

Table 3
A comparison of patients with hematologic and solid organ malignancy who had febrile neutropenia.

	Hematologic malignancy number (%)	Solid organ malignancy number (%)	P value
Number	210	161	
Mean age	46.9 (23.4)	45.1 (21.3)	0.45
Female	86 (40.9)	100 (62)	<0.001
Severe neutropenia	78 (37.1)	70 (43.5)	0.21
CVC	65 (31)	53 (33)	0.68
Bacteremia	36 (17.1)	14 (8.7)	0.042
Urine positive culture	8 (3.8)	5 (3.1)	0.91
CXR with infection	173 (82.3)	127 (78.9)	0.16
Mortality	26 (12.4)	15 (9.3)	0.35

CVC: central venous catheter; CXR: Chest X-ray

A comparison between those who survived and those who died showed that mortality was significantly associated with the presence of bacteremia 24.4% versus 12.4% in the abscence of bactermia (P = 0.016) (Table 2). There was no significant association of mortality with age, type of malignancy, presence of central venous catheter, or the severity of neutropenia.

Compared to patient with hematological malignancy, patients with solid organ malignancy were more likely to be female 62% versus 14.9% (P < 0.001) and were less likely to have bacteremia 8.7% versus 17.1%, P = 0.042 (Table 3).

Discussion

We found that 13% of the febrile neutropenia episodes had positive blood cultures with equal frequency of Gram-negative bacilli (5.4%) and gram positive cocci (5.1%). It is estimated that bacteremia occurs in 10–25% of febrile neutropenic patients especially in those with prolonged or severe neutropenia [1,2,10]. The rate of bacteremia was 37% among childhood febrile neutropenia [11], 19% in another study in Saudi Arabia [7] and 18% in a study from Lebanon [12]. In a study of 71 patients with febrile neutropenia in KSA, positive blood cultures were higher in hematologic malignancy (68%) vs. solid organ malignancy (16%) [6]. Of the 21 positive blood cultures, 14 (66.7%) were gram-positive bacteria, 5 (23.8%) were gram-negative bacteria, and 4 (19%) were fungi [6]. In another small study of 56 patients, 16.4% had positive cultures and there was 7.5% gram-positive bacteria, 7.5% gram-negative bacteria and 1.5% fungi [5]. The proportion of gram negative bacteria was higher in a study from Lebanon [12]. Previous studies from Lebanon showed greater gram negative bacterial infections compared to higher gram positive bacterial infections in patients with febrile neutropenia in Kuwait, United Arab Emirates and Saudi Arabia [6,11–15]. These differences might be related to the different population and the extent of use of central lines in the included patients.

It is interesting to note that there was a small number of patients who had candidemia during the episodes of febrile neutropenia. In our hospital, the annual incidence of candidemia was 0.2–0.76 cases/1000 hospital discharges and 0.45–1.6/10,000 patient-days per year [16]. Neutropenia accounted for 9% of all candidemia episodes [16]. The overall mortality rate in this cohort was 11.2%. In a previous study from Saudi Arabia, the mortality rate was 19.2% among patients treated with empiric ceftazidime and amikacin [15]. And the reported mortality rate was similar to those figures from Lebanon and slightly higher than a rate of 4–7% in other studies [12]. It had been shown that gram negative bacilli bacteremia is associated with a higher rate of mortality [2,10].

The most frequently used single antimicrobial agents were imipenem (38%) and ceftazidime (7.5%), and other patients received variable combination therapy. Thus, the compliance with single antimicrobial therapy was 45.5% in this study, consistent with other studies. In a previous study from Saudi Arabia, compliance with recommended therapy was 45% [7]. The variability in the compliance rate with the recommended therapy may be related to patients' characteristics, the presence of previous antibiotic resistance or the severity of febrile neutropenia. These factors were not examined in this study.

In conclusion, we had shown that febrile neutropenia in this study has a low rate of bacteremia and that about 45% received the recommended initial empiric therapy. Bacteremia was documented in 13.5% with equal frequency of Gram-negative bacilli and gram positive cocci. Further studies are needed to evaluate risk factors for gram negative bacilli vs. gram positive cocci bacteremia in this population with febrile neutropenia.

Competing interests

None declared.

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