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Patterns of Bacterial Isolates and their Resistance to Antibiotics in Patients with Chemotherapy-induced Febrile Neutropenia at a University Hospital

Said Ahmed Al Saifi[1]*, Badriya Al Adawi[2] and Ikram Burney[3]

[1]Division of Radiation Oncology, Department of Radiology, University of Ottawa, Ottawa, Ontario, Canada
[2]Department of Microbiology and Immunology, Sultan Qaboos University Hospital, Muscat, Oman
[3]Department of Medicine, Sultan Qaboos University Hospital, Muscat, Oman

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ABSTRACT

Objectives: Febrile neutropenia is a major complication of cytotoxic chemotherapy and is associated with a high rate of mortality and morbidity if not treated appropriately. Consequently, it is important to know the bacterial spectrum and pattern of its resistance in each hospital to formulate an appropriate empiric antibiotic regimen. We sought to study the bacterial spectrum in patients with chemotherapy-induced neutropenia and report their resistance patterns. ***Methods***: We conducted a retrospective study on patients admitted with febrile neutropenia between January 2010 and December 2016 in the oncology unit at Sultan Qaboos University Hospital in Oman. Consecutive patients diagnosed with non-hematological malignancies who had febrile neutropenia and positive blood culture were included in this study. ***Results:*** A total of 76 bacterial isolates were documented in 67 episodes in 62 patients. There were 26 male and 36 female patients. The median age was 51 (14–81) years. The most common cancers were breast cancer (17.7%), non-Hodgkin lymphoma (16.1%), and colon cancer (14.5%). Gram-negative and gram-positive organisms accounted for 73.7% and 26.3% of all isolates, respectively. The most common gram-negative organisms were *Pseudomonas aeruginosa* (26.8%), *Escherichia coli* (23.2%), *Klebsiella* species (17.9%), and *Acinetobacter baumannii* (12.5%). The most common gram-positive organisms were *Staphylococcus aureus* (30.0%), followed by coagulase-negative *Staphylococcus* (25.0%). There were 14 multidrug-resistant organisms and eight extended-spectrum beta-lactamases (ESBL). The resistance among gram-negative organisms to the commonly used broad-spectrum antibiotics was 23.5–55.6%. No resistance was recorded against vancomycin amongst the gram-positive organisms. Eight (12.1%) patients died while neutropenic. ***Conclusions:*** Gram-negative organisms were the predominant organisms. There is a high rate of resistance to the commonly used antibiotics. Using a combination of antibiotics is warranted in patients presenting with chemotherapy-induced febrile neutropenia.

Febrile neutropenia is a medical and oncological emergency.[1] Patients presenting with presumed febrile neutropenia need urgent evaluation and empiric broad-spectrum antibiotics.[2] Febrile neutropenia is defined as a single oral temperature of > 38.3°C or a temperature of >38.0°C sustained for more than one hour in the presence of an absolute neutrophil count (ANC) of < 500 cells/μL or an ANC that is expected to decrease to < 500 cells/μL within the next 48 hours.[3] Cytotoxic chemotherapy is the most common cause of febrile neutropenia and accounts for 90% of cases.[3] Between 10–50% of patients with solid tumors receiving cytotoxic chemotherapy may develop febrile neutropenia.[4]

Bacteremia occurs in 10–25% of all patients receiving chemotherapy for non-hematological malignancies; most episodes occurring in the setting of prolonged or profound neutropenia (ANC < 100 /μL).[5,6] Several studies suggest that gram-positive organisms are more common.[4] Also, several guidelines suggest that single-agent broad-spectrum antibiotics covering the gram-negative organisms may suffice as the initial empiric antibiotic therapy. However, a universal guideline for empiric antibiotic use for the treatment of febrile neutropenia cannot be

*Corresponding author: ikram@squ.edu.om; ikramburney@hotmail.com

applied because the causative organisms and pattern of resistance to antibiotics may differ from one institution to another. As a result, each institution should develop its own guidelines, review those periodically, and the physicians should be aware of the local bacterial isolates and their pattern of microbial resistance.[7]

This analysis aimed to study the types of bacterial isolates and resistance patterns to commonly used antibiotics in patients receiving cytotoxic chemotherapy who were admitted with febrile neutropenia in the medical oncology unit at our institution. The result may help in modifying the current empiric antibiotic regimen in this setting.

METHODS

This was a retrospective study conducted on patients age > 14 years old, admitted to the oncology wards at Sultan Qaboos University Hospital (SQUH) between January 2010 and December 2016. Electronic Patient Records of consecutive patients diagnosed with cancer and admitted with a diagnosis of febrile neutropenia and a documented bacterial infection during the episode were identified and reviewed. Patients with hematological malignancies such as leukemia, multiple myeloma, and those with autoimmune disorders were excluded. Also, patients who did not have bacterial isolates despite being neutropenic and febrile, or did not fulfill the criteria of febrile neutropenia were excluded. The study was approved by the ethics committee of the College of Medicine and Health Sciences at SQU.

The bacterial cultures reported from blood, urine, sputum, abscess, stool, or any other foci of infection were reviewed. Information on the demographic features of the patients, the type and stage of malignancy, type of chemotherapy, the time between chemotherapy and occurrence of febrile neutropenia, risk factors such as the presence of indwelling catheters, comorbidities, and outcomes of the episode were extracted. The data were stored and analyzed using SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

All samples were processed in the diagnostic microbiology laboratory at SQUH. For each sample type, the choice of culture media, incubation atmosphere, incubation temperature, and incubation time were all based on the local standard operating procedures. Blood cultures were processed using the BACTEC™ system (Becton Dickinson, USA). Identification and antimicrobial susceptibility testing of significant isolates was done using a combination of methods depending on the organism type. Due to the nature of the study, there may have been minor variation in the lab methods used over the six-year study period. In general, gram-negative bacilli (other than *Haemophilus* and *Moraxella*), *staphylococci*, and some *enterococci* and *streptococci* were identified and tested for susceptibilities using the automated system Phoenix™ (Becton Dickinson, USA). *Haemophilus* species, *Moraxella* species, and the remaining *enterococci* and *streptococci* were identified using a combination of methods (catalase, oxidase, satellitism, X and V factor requirement, Lancefield grouping, bile-esculin test, and analytical profile index. Susceptibility testing was done using disc diffusion and gradient diffusion methods (when required). Susceptibility results for all organisms were based on Clinical Laboratory Standards Institute breakpoints available for that period.

In general, gram-positive organisms were tested for susceptibility to penicillin, oxacillin, ampicillin/amoxicillin, and vancomycin. Gram-negative organisms were tested for piperacillin-tazobactam, ceftazidime, cefepime, meropenem, colistin, tigecycline, cotrimoxazole, ciprofloxacin, gentamicin, and amikacin. Multi-drug resistant organisms (MDRO) were defined as organisms resistant to at least three classes of antibiotics, including penicillins, cephalosporins, carbapenems, aminoglycosides, and quinolones. Organisms isolated from surveillance cultures were excluded.

Mortality was considered attributable to the febrile neutropenic episode if the death occurred while the patient was still febrile and neutropenic, even in the presence of other discernible causes of death, such as pulmonary embolism or acute kidney injury.

The results are expressed in actual numbers as well as percentages related to the gram-negative and gram-positive organisms separately. In all other cases, the denominator is explained separately.

RESULTS

Sixty-seven episodes of febrile neutropenia were identified in 62 patients with non-hematological malignancies over the study period. During those episodes, 76 bacterial isolates were identified. The

Table 1: Demographic features.

Variables	n (%)
Total number of patients	62
Total number of episodes	67
Total number of isolates	76
Age (median), years	51 (14–81)
Gender	
Male	26 (41.9)
Female	36 (58.1)
Body mass index	25.0
Diagnosis	
Breast cancer	11 (17.7)
Non-Hodgkin lymphoma	10 (16.1)
Colon cancer	9 (14.5)
Stomach cancer	6 (9.7)
Sarcoma	6 (9.7)
Ovarian cancer	3 (4.8)
Hodgkin lymphoma	3 (4.8)
Others	14 (22.6)*
Clinical stage of cancer	
I	7 (11.3)
II	8 (12.9)
III	10 (16.1)
IV	37 (59.7)

**Others include two cases of larynx cancer, germ cell tumor, choriocarcinoma and small cell lung cancer, and one case of parathyroid cancer, cervix cancer, glioblastoma, neuroendocrine tumor, bladder cancer, and maxillary cancer.*

median age of patients was 51 (14–81) years. There were 26 (41.9%) males and 36 (58.1%) females. The most common cancers were breast cancer (17.7%), non-Hodgkin lymphoma (16.1%), and colon cancer (14.5%). The underlying diagnosis and clinical stage of the disease at the time of presentation are shown in Table 1.

The details of chemotherapy treatment are shown in Table 2. The vast majority of patients received docetaxel and doxorubicin-based chemotherapy. Twenty (29.9%) patients received 5-fluorouracil-based and ifosfamide-based chemotherapy.

Febrile neutropenia was reported 11.5 days (mean) after receiving chemotherapy. During the 67 episodes, 43 (64.2%) patients received prophylactic granulocyte-colony stimulating factor (G-CSF), whereas 22 (32.8%) patients did not receive prophylactic G-CSF.

Out of the 67 episodes, indwelling venous catheters were present during 26 episodes. The mean duration of hospitalization was 8.8 days. Of the 62 patients, 11 required inotropic support and 11 had to be shifted to the intensive care unit because of

Table 2: Baseline clinical and laboratory features.

Chemotherapy type	n (%)
Docetaxel and/or doxorubicin-based	17 (25.4)
5-fluorouracil-based	13 (19.4)
Ifosfamide-based	7 (10.4)
Gemcitabine-based	5 (7.5)
BEP	4 (6.0)
R-CHOP	4 (6.0)
Others ¥	17 (25.4)
Episode features	
Days after chemotherapy	11.5
G-CSF before discharge	
Yes	43 (64.2)
No	22 (32.8)
Missing data	2 (3.0)
Presence of central venous catheter	
Yes	26 (38.8)
No	41 (61.2)
WBC	1.2×10^9/L
ANC	0.33×10^9/L
Platelets	143×10^9/L
Hemoglobin	9.54 gm/dL

BEP: bleomycin, etoposide, and cisplatin ; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
¥Others: three ABVD (doxorubicin, bleomycin, vinblastine, and DTIC) and PMiTCEBO (prednisolone, mitaxantrone, cyclophosphamide, etoposide, bleomycin, vincristine), two R-ICE (rituximab, ifosfamide, carboplatin, etoposide), vinorelbine and cisplatin and paclitaxel-based and one each of high dose methotrexate and rituximab, hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone), irinotecan and 5-fluorouracil, doxorubicin, and cyclophosphamide.
G-CSF: granulocyte-colony stimulating factor; WBC: white blood cell; ANC: absolute neutrophil count.

sepsis secondary to febrile neutropenia. A total of eight patients died while they were neutropenic and septic [Table 3].

The details of the bacterial isolates are shown in Table 4. Overall, a total of 20 gram-positive bacteria and 56 gram-negative bacteria were isolated. The most common organisms were *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* accounting for 26.8%, 23.2%, and

Table 3: Clinically relevant outcomes of patients admitted with febrile neutropenia.

Variables	n (%)
Days in hospital	8.8
Need for ionotropic support	11/62 (17.7)
Admission to the intensive care unit	11/62 (17.7)
Death	8/62 (12.9)

Table 4: Bacterial isolates, frequency, and source in patients admitted with febrile neutropenia.

Bacteria	Frequency	Blood	Swab	Urine	Sputum	Peritoneal fluid	Stool
Gram-negative (73.7%)							
Pseudomonas aeruginosa	15	4	7	2	2	0	0
Escherichia coli	13	8	1	5	0	0	0
Klebsiella species	10	2	3	3	2	0	0
Acinetobacter baumannii	7	1	2	2	1	1	0
Haemophilus species	3	0	0	0	3	0	0
Salmonella species	2	1	0	0	0	0	1
Enterobacter species	2	1	1	0	0	0	0
Others*	4	2	0	0	2	0	0
Gram-positive (26.3%)							
Staphylococcus aureus	6	0	6	0	0	0	0
Coagulase-negative staphylococcus	5	5	0	0	0	0	0
Streptococcus pneumoniae	3	2	0	0	1	0	0
Enterococcus faecium	2	1	0	1	0	0	0
Others†	4	2	0	1	0	1	0
Total‡	76	29	20	14	11	2	1

*Others: One Moraxella, Stenotrophomonas maltophilia, Ochrobactrum anthropi, and Pseudomonas species.
†Others: One Streptococcal, Diphtheroid, Streptococcus agalactiae, and Enterococcus faecalis.
‡One organism was isolated from blood and urine during the same episode.

17.9% of the gram-negative organisms, respectively. *Staphylococcus aureus* was the most commonly isolated gram-positive organism.

Amongst the gram-positive organisms, two out of six (33.3%) *Staphylococcus aureus* isolates were methicillin-resistant. Amongst the gram-negative organisms, eight (14.3%) organisms were extended-spectrum beta-lactamase (ESBL), and three (5.4%) organisms were carbapenem-resistant *Enterobacteriaceae*. Fourteen (25.0%) had resistance to three groups of antibiotics and were labeled as MDRO.

The pattern of resistance for gram-negative organisms to the commonly used antibiotics is shown in Table 5. It can be seen that the resistance for commonly used antibiotics (i.e., piperacillin-tazobactam, meropenem, third-generation cephalosporins, quinolones, and aminoglycosides)

Table 5: Pattern of resistance to commonly used antibiotics in patients admitted with febrile neutropenia.

Antibiotics	Sensitive (%)	Resistant (%)	Intermediate (%)
Gram-negative organisms			
Piperacillin-tazobactam	38 (69.1)	16 (29.1)	1 (1.8)
Meropenem	37 (72.5)	12 (23.5)	2 (3.9)
Cefepime	17 (43.6)	21 (53.8)	1 (2.6)
Ceftazidime	27 (51.9)	23 (44.2)	2 (3.8)
Ciprofloxacin	24 (50.0)	22 (45.8)	2 (4.2)
Co-trimoxazole	20 (44.4)	25 (55.6)	0 (0.0)
Amikacin	38 (74.5)	13 (25.5)	0 (0.0)
Gentamicin	29 (55.8)	23 (44.2)	0 (0.0)
Colistin	36 (100)	0 (0.0)	0 (0.0)
Tigecycline	6 (60.0)	3 (3.0)	1 (1.0)
Gram-positive organisms			
Vancomycin	20 (100)	0 (0.0)	0 (0.0)
Oxacillin	4 (36.4)	7 (63.6)	0 (0.0)
Ampicillin	3 (33.3)	6 (66.7)	0 (0.0)
Penicillin	5 (35.7)	8 (57.1)	1 (7.1)

Table 6: Pattern of bacterial isolates with selected regional and international studies.

Study	Country	Tumor type	Gram-positive	Gram-negative
Anatoliotaki et al, 2004[12]	Greece	Solid tumors	44	51
Zahid et al, 2009[13]	Pakistan	Solid and hematological malignancies	42.3	57.6
Huang et al, 2011[14]	Taiwan	Solid and hematological malignancies	33	63
Sirkhazi et al, 2014[15]	Saudi Arabia	Solid tumors	28.9	71.1
Marin et al, 2014[16]	Spain	Solid tumors	31.4	60.5
Babu et al, 2016[17]	India	Solid and hematological malignancies	40	58
Ikram Burney et al (this study)	Oman	Non-hematological malignancies	26.3	73.7

ranged between 23.5% and 55.6%. On the other hand, there was no report of resistance to vancomycin amongst the gram-positive organisms.

DISCUSSION

To the best of our knowledge, this is the first study from Oman to report the bacterial isolates and resistance patterns in patients with chemotherapy-induced febrile neutropenia. SQUH receives patients from all over Oman, hence, it will be reasonable to think that the pattern of resistance to antibiotics reflects the pattern amongst such patients in the country. Almost two-thirds of isolates were gram-negative organisms, with *Pseudomonas*, *E. coli*, *Klebsiella*, and *Acinetobacter* being the most frequent. Between 23.5% and 55.6% of the isolates were resistant to the most frequently used broad-spectrum bactericidal antibiotics commonly used to treat gram-negative bacteremia and sepsis. Twenty-five percent were MDROs.

For several years, gram-negative organisms were the most commonly identified organisms in patients with chemotherapy-induced febrile neutropenia.[2,8] After almost two decades, there was a shift to gram-positive organisms.[9] This was attributed to the increased use of central venous catheters, dose-intense chemotherapy cycles leading to mucositis, and the frequent use of fluoroquinolones for prophylaxis of fever and sepsis.[10,11] This study revealed that the majority (73.7%) of the isolates were gram-negative organisms. Our results are consistent with reports from Greece, Pakistan, Spain, Taiwan, Saudi Arabia, and India [Table 6].[12–17] Our results are at variance with reports from the UK, where gram-positive organisms are still the predominant cause of bacteremia in hematological and non-hematological malignancies.[18]

Globally, there is an increase in bacterial resistance to the commonly used antibiotics, including patients with both hematological and non-hematological malignancies.[19] Amongst other reasons, organisms with intrinsic resistance to antibiotics have increased compared to the era before 1990.[20] In this study, the number of ESBL and MDRO was 8 and 14 (14.3% and 25.0% of the gram-negative organisms, respectively). There was also a high percentage of resistance to the commonly used empiric antibiotics with bactericidal activity. For example, 29.1% of the gram-negative organisms were resistant to piperacillin-tazobactam, and 44.2% of *E. coli* were resistant to gentamicin. Our results are consistent with Burney et al,[10] who showed that a significant majority of *E. coli* were resistant to piperacillin, and Babu et al,[17] showed that the overall sensitivity of gram-negative bacilli to piperacillin-tazobactam was 60%. In comparison, approximately 40% of *Acinetobacter baumannii* and *Klebsiella pneumoniae* were resistant to meropenem. However, the results are at variance with a study published from the UK, which showed that only 5% of isolates were resistant to piperacillin-tazobactam amongst patients with non-hematological malignancies.[18]

The high percentage of resistance among gram-negative organisms in this study has several implications. Firstly, it would be safer to use a combination of non-cross resistant antibiotics, rather than a single agent, as is suggested by some guidelines published from North America and western Europe, especially in patients with high-risk febrile neutropenia.[4,7] Secondly, a low threshold should be maintained to modify the initial empiric antibiotic regimen. Thirdly, the results underscore the importance of obtaining specimens for culture more frequently to make rational decisions while modifying the antibiotics. Finally, it highlights the

importance of studying the spectrum of isolates and their resistance patterns in institutions frequently involved in managing chemotherapy-induced febrile neutropenia.

The mortality rate in this study was 12.1%. Several factors could explain this high mortality rate. First of all, the mortality rate was calculated in patients who had a documented bacterial isolates. Patients with febrile neutropenia without isolates were not included. Our results are consistent with studies from Taiwan, UK, and the USA, which showed a similar mortality rate to ours (12%, 12.5%, and 11%, respectively) in patients with chemotherapy-induced febrile neutropenia.[14,21,22] On the other hand, the mortality rate reported from studies from India (4% in solid tumors) was significantly lower than the 12% reported in this study.[17] However, the denominator needs to be mentioned. The study by Babu et al,[17] reported on the isolates and mortality rates from 379 episodes of febrile neutropenia, of which 143 (38%) were in solid tumors. Out of 143 episodes of febrile neutropenia, only 34 had a documented bloodstream infection. A total of 14 patients died. Hence, of the solid tumors, the mortality was around 10% (14/143), whereas, out of those with a documented bloodstream infection the rate was even higher 41% (14/34). It is important to carefully look at the denominator while comparing the outcomes. Second, most of the patients in our study had end-stage disease. Almost 60% of the patients were receiving palliative chemotherapy when they developed febrile neutropenia. For several patients, the course of febrile neutropenia was complicated by renal failure, deep vein thrombosis, and hepatitis. Moreover, some of the patients grew more than one organism. Advanced stage disease and comorbidities, such as shock at presentation, are known to be associated with high mortality in patients with non-hematological malignancies.[23]

There are a few limitations of this study. First, the study was carried out on episodes from 2010 to 2016. Over the study period, the bacterial spectrum and pattern of resistance may have changed. However, the high rate of resistance to certain antibiotics, such as ceftazidime, has been reported from SQUH previously, and continues to be so in febrile neutropenic patients also. Second, while 38.2% of the bacteria identified in this study were grown from blood and hence are clinically significant, 59% were grown from non-sterile sites (swab, urine, and sputum) where they could represent either colonization or infection. However, as is clear from the clinical parameters and the outcomes, bacteria isolated from other sites were clinically relevant in this study.

CONCLUSION

Gram-negative organisms are the most common cause of febrile neutropenia in our institution. There was a high percentage of resistance to the commonly used bactericidal antibiotics. For this reason, a combination of antibiotics is strongly recommended.

Disclosure

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