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Identification of Risk Factors Associated with Microbiologically Diagnosed Infections, and Mortality in the Cases of Pediatric Febrile Neutropenia: A Cross-Sectional Study

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Abstract

Aim: To identify the risk factors associated with microbiologically diagnosed infections (MDI), and mortality in the cases of pediatric febrile neutropenia

Study design: A cross-sectional study

Place and Duration: This study was conducted at Pakistan Institute of Medical Sciences Islamabad, Pakistan from June 2020 to June 2021.

Methodology: The current study involved 414 episodes of febrile neutropenia in 264 children, who were less than 12 years of age, and predictive high-risk factors were assessed. The study included children who had experienced febrile neutropenia after getting the chemotherapeutic treatment in the hospital. Exclusion criteria included children who were going through stem cell therapy, were receiving palliative care, and the patients who had febrile neutropenia when they were diagnosed with cancer.

Results: The current study identified that MDIs were present in 82 children out of which 14.2% had bacterial infections, and 4.3% had fungal. The complications were present in 109 children out of which 43 died; 35 children died due to bacterial sepsis whereas 8 died because of fungal sepsis.

Conclusion: In the children having febrile neutropenia, the concentration of C - reactive protein more than 90 mg/dL, platelet concentration less than 20000/uL, and albumin concentration less than 2.5 g/dL were considered as high-risk factors for mortality, complications, and prolonged hospital stays.

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Keywords: Febrile neutropenia, microbiologically diagnosed infections, C - reactive protein

Introduction

Neutropenia associated with chemotherapy is a common cause of infections in children and concerns most pediatric oncologists. For that reason, aggressive management is necessary which includes the prescription of antibiotics, immediate hospitalization, and close monitoring of the patients.[1] These preventive measures have considerably reduced the mortality rate associated with febrile neutropenia induced by chemotherapy. Febrile neutropenia and a microbiologically documented infection increase the rate of complications, duration of hospital stay, and the chances of death.[2] This study was designed to assess the risk factors associated with microbiologically documented infections, prolonged stays in hospitals, and reasons for mortality in children who have developed febrile neutropenia after chemotherapy.

Methodology

The current study was conducted on the children of less than 12 years of age admitted at our hospital. The study included children who had experienced febrile neutropenia after getting the chemotherapeutic treatment in the hospital. Informed consent was obtained from all the patients and their guardians. Permission was taken from the ethical review committee of the institute. Exclusion criteria included children who were going through stem cell therapy, were receiving palliative care, and the patients who had febrile neutropenia when they were diagnosed with cancer. Empirical therapy included broad-spectrum antibiotics administered intravenously which included cefoperazone-sulbactam (50 mg/kg) given at the interval of 8 hours and amikacin (15 mg/kg) given per day. Once the venous blood was drawn, tests for C-reactive protein (CRP), complete blood count, and blood culture were conducted for all patients. Observing the clinical presentations, different cultures were also obtained from different sites. Patients who had hemodynamic compromise were asked to start carbapenem along with vancomycin with an interval of 8 hours per day. The treatment of antibiotics started within an hour of the presentation of symptoms. Voriconazole was recommended for fungal prophylaxis. If the fever was persisted for more than 48 hours, repeat cultures of the patients were conducted. In all the children suffering from prolonged febrile neutropenia, CT scans of the chest were conducted in the intense phases of therapy to observe hematological malignancies. For children whose febrile neutropenia was in the maintenance phase and for the individuals who have solid tumors, CT scans were performed. Imaging of different parts such as the abdomen, sinus, or brain was also performed depending upon the symptoms, and histological confirmation was conducted on the basis of lesion accessibility. The presence of galactomannan in serum was evaluated in all the children who were experiencing prolonged febrile neutropenia and having underlying hematological malignancies. Microbiologically documented infection was defined as a positive culture obtained from a body compartment or fluid which is usually sterile and the results are validated by the presence of an antigen or a positive PCR test. According to EORTC/MSG-2008, invasive fungal diseases were characterized as probable, possible, and proven infections. If there was a history of non-upper respiratory focus of infection was taken into consideration. Similarly, clinical examination of other foci was conducted such as chest signs were examined when the lower respiratory tract was involved, in cases of rash, nodules, or ulcers cutaneous manifestations were observed, and diarrhea and abdominal pain was considered when the gastric or central nervous system was involved. When patients complained of abdominal pain along

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with febrile neutropenia, neutropenic enterocolitis was detected. Similarly, the thickness of the bowel wall was also observed by the ultrasound or CT scans. Perianal sepsis was confirmed when perianal soft tissue was inflamed. UTI was recommended when a positive urine culture was obtained in a child. In case of complications, before antimicrobial therapy, the active intervention was performed. Data were analyzed by using SPSS version 23.

Results

The current study included 414 febrile neutropenia episodes that occurred in a total of 264 children. The average age recorded for the children was 5 years with an observed male to female ratio of 3:1. Most of the children 367 (88.6%) had hematological malignancies. The characteristics of patients are presented in Table number 1. E. coli was isolated in 12 cases, S. aureus in 9 cases, and K. pneumonia in 7 cases. Most of the organisms were isolated from blood (94%), then urine (3%), pus (1.5%), and ear discharge (1.5%). Underlying hematological malignancies were observed in all the patients having IFD. Out of 13 patients, 6 patients were in the proven category, 6 in the probable category, and 4 in the possible category. The identified fungi included Aspergillus, Pseudallescheria, Mucor, and Candida. Out of 414 episodes, 26% (109) had complications which included respiratory failure (12%), fluid refractory shock (12%), acute injury of kidneys (4.5%), encephalopathy (3.9%), and neutropenic enterocolitis (5.3%). It was observed that the rate of mortality was 10.3%, out of which 8 individuals had IFD, and 35 had bacterial sepsis. It was also found that IFD had caused 50% mortality in patients. The average duration of hospital stay was seven days in patients who died and five days in patients who were discharged. It was also observed that 65% of patients stayed in the hospital for less than or equal to 5 days, out of which 252 (93%) were discharged, and 18 patients died. Of the patients who stayed for more than 5 days, 119 patients were discharged and 25 patients died in the hospital. It was also observed that individuals having MDI complications experienced more complications as compared to the ones with no MDI, had prolonged stay i.e. more than 5 days, and mortality rates were higher among them. Factors that predicted MDI on the univariate analysis included chemotherapy interval, diagnosis of acute myeloid leukemia, presence of central venous line, and undernutrition as indicated in table number 1. Similarly, for the multivariate analysis, the predictors included chemotherapy interval are described in table number 2.

Table 1: Characteristics and outcomes of patients having febrile neutropenia (n=414)

Parameters	N (%)
Males	315 (76)
Solid tumors	47 (11.4)
Hodgkin lymphoma	6 (1.4)
Acute lymphoblastic leukemia	307 (74.2)
Acute myeloid leukemia	38 (9.2)
Chemotherapy intervals less than or equal to 7 days	141 (34.1)
Intensive chemotherapy phase	279 (67.4)
Temperature less than or equal to 39ºC	132 (32)
Undernutrition	70 (16.9)
Infection’s clinical focus	166 (40)
Upper respiratory focus	57 (13.7)

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Non-upper respiratory focus	109 (26.3)
Hemoglobin less than or equal to 70 g/L	56 (13.5)
Absolute neutrophil count less than or equal to 100/µL	130 (31.4)
Platelet count less than 20000/L	165 (60.1)
C-reactive protein more than 90 mg/L	145 (35)
Albumin less than 2.5 g/dL	35 (8.5)
Discharged within 5 days of admission	252 (60.9)
Discharged after 5 days of admission	119 (28.7)
Died	43 (10.4)
Microbiologically documented infections	82 (19.8)
Bacterial infections	65 (79.3)
Invasive fungal infections	16 (19.5)
Combined bacterial and fungal infection	1 (1.2)
Complications	109 (26.3)
Fluid refractory shock	50 (12)
Respiratory failure	50 (12)
Encephalopathy	16 (3.9)
Different metabolic complications	64 (15.4)
Renal failure	19 (4.5)
Neutropenic enterocolitis	22 (5.3)
Congestive cardiac failure	3 (0.7)
Coagulopathy and bleeding	2 (0.5)
Gangrene	1 (0.2)
Pleural effusion	1 (0.2)
Liver abscess	1 (0.2)
A complication that requires intensive care	28 (6.7)

Table 2: Risk factors for MDI

Risk factors	Outcome	P-value
For MDI		
AML diagnosis	1.71 (0.67-4.29)	0.25
Chemotherapy interval less than or equal to 7 days	3.60 (1.69-7.64)	0.001
Non-URI focus of infection	1.96 (1.12-3.41)	0.015
Temperature more than or equal to 39 ºC	1.67 (0.51-5.43)	0.39
Central venous line	0.81 (0.36-1.81)	0.60
Under nutrition	1.25 (0.63-2.49)	0.51
Platelet less than or equal to 20000/µL	2.18 (1.04-4.54)	0.03
Hemoglobin less than or equal to 70 g/L	0.76 (0.44-1.32)	0.33
ANC less than or equal to 100/ µL	0.85 (0.40-1.79)	0.67
C-reactive protein more than 90 g/L	1.71 (0.85-3.44)	0.13
Albumin less than 2.5 g/dL	1.16 (0.48-2.84)	0.73

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For mortality		
Chemotherapy interval less than or equal to 7 days	18.91 (2.34-152.52)	0.006
Non-URI focus of infection	6.10 (2.5-15.0)	<0.001
Temperature less than or equal to 39ºC	1.24 (0.28-5.53)	0.77
Hemoglobin less than 70 g/L	0.45 (0.15-1.35)	0.15
Platelets less than 20000/uL	2.18 (1.04-4.54)	0.03
ANC less than or equal to 100/uL	2.69 (0.71-10.21)	0.14
C-Reactive protein more than 90 mg/L	8.17 (2.21-30.24)	0.02
Albumin less than 2.5 g/L	3.03 (1.07-8.609)	0.04
For hospital stay of more than 5 days		
AML diagnosis	3.40 (1.41-8.34)	0.007
Chemotherapy interval for less than or equal to 7 days	1.77 (1.10-2.85)	0.02
Non-URI focus of infection	1.38 (0.88-2.17)	0.16
Temperature more than or equal to 39ºC	1.65 (0.62-4.38)	0.31
Central venous line	1.46 (0.76-2.8)	0.25
Platelets less than or equal to 20000/uL	1.81 (0.98-3.35)	0.057
ANC less than or equal to 100/uL	1.63 (0.97-2.71)	0.06
C-Reactive Protein more than 90 mg/L	2.21 (0.79-6.17)	0.13
Albumin less than 2.5 g/dL	1.87 (0.82-4.30)	0.14

Discussion

Out of all the patients 19.8% had MDIs, among which 26% had developed different complications. We also observed that 28.7% of patients were discharged from the hospital after 5 days, and 10.3% of patients died. Platelet count was recorded as an additional MDI predictor whereas albumin and CRP were recorded as they were associated with high mortality. More stay in hospital in adults having febrile neutropenia associated with cancer was predicted by multi-resistant bacteria and hematological malignancy.[3] When AML was diagnosed in children, it predicted that the stay in hospital would be for more than 5 days.[4] However, patients who had Hodgkin lymphoma, ovarian or testicular cancer, or soft tissue sarcoma experienced shorter stays in the hospital.[5] In a study conducted in Chile, the time recorded since the last chemotherapy which is less than or equal to 7 days was used as a predictive measure for invasive bacterial sepsis.[6] A study conducted in Brazil suggested that a clinically identified focus can predict serious issues in individuals.[7] A study conducted by Mueller et al identified that acute otitis media and upper respiratory tract infection are associated with a short stay in hospital.[5] Moreover, thrombocytopenia was also found to be associated with MDIs.[7] It is suggested that thrombocytopenia is considered as a surrogate marker to identify the increased consumption and marrow suppression in sepsis. One of the prediction markers of inferior outcomes in febrile neutropenia is low albumin. C - reactive protein is also considered an inexpensive biomarker used to identify febrile neutropenia. There is an association reported between the duration of febrile neutropenia and elevated C-reactive protein [8]. To assess antibiotic therapy in children having febrile neutropenia, and to diagnose bacterial infections, the serial monitoring of C-reactive protein is a useful biomarker as indicated in a study conducted in India.[9,10] Another similar study reported that C - reactive protein is the strongest predictor used to predict febrile neutropenia in children.[11,12] Identifying these risk factors can help to sort and identify patients who are at high risk

so that their disorders can be timely managed. It is suggested that thrombocytopenia is considered as a surrogate marker to identify the increased consumption and marrow suppression in sepsis. One of the prediction markers of inferior outcomes in febrile neutropenia is low albumin. C - reactive protein is also considered an inexpensive biomarker used to identify febrile neutropenia

The current study was conducted prospectively and had 414 episodes of febrile neutropenia. These episodes were treated uniformly by using the same strict protocol. Although, as this study was conducted in only one hospital so there is a chance that the results obtained were less relevant. Although the obtained results could vary in the low, middle, or high-income countries.

Conclusion

In the children having febrile neutropenia, the concentration of C - reactive protein more than 90 mg/dL, platelet concentration less than 20000/uL, and albumin concentration less than 2.5 g/dL were considered as high-risk factors for mortality, complications, and prolonged hospital stays

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