Febrile neutropenia in nonmalignant conditions: tertiary center experience

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Background
Neutrophils play an important role in immunity of the body because they attack and kill the invading microorganisms. The clinical sequelae of neutropenia usually manifest as infections, most commonly of the mucous membranes. The risk of serious infection increases as the absolute neutrophililc count falls to the severely neutropenic range (<500/μl).

Patients and methods
A retrospective study was conducted on patients admitted to Haematology Unit and Intermediate Care Unit at Assiut University Children Hospital during the period from April 1, 2018 to March 31, 2019 (1-year study). Data were collected and compared with guidelines.

Results
Among 50 patients, males were 44% and females were 56%. All patients enrolled in this study were neutropenic and had fever. Patients having neutropenia due to aplastic anemia were 92%, patients having oral mucosal lesions were 56%, and patients having fever of unknown origin were 44%.

Conclusion
Aplastic anemia is the most common cause of nonmalignant febrile neutropenia. Neutropenia leads to severe infections. Granulocyte colony-stimulating factor can be used in treatment of neutropenia. Bone marrow transplant can cure this disorder.

Keywords:
aplastic anemia, febrile neutropenia, immune deficiency, neutropenia

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Introduction

Neutrophils play an important role in immune defenses because they ingest, kill, and digest invading microorganisms, including fungi and bacteria [1–3]. Failure to carry out this role leads to immunodeficiency that is mainly characterized by the presence of recurrent infections [4]. Defects in neutrophil function can be quantitative as seen in neutropenia or qualitative as seen in neutrophil dysfunction. The standard circulating neutrophil count is above 1.5×10^9/l. Neutropenia can be classified into asymptomatic (mild), moderate, and severe, and thus the progression to infection is related to the number [1].

Neutrophils belong to the phagocyte system and represent the first cellular components of the inflammatory response and key components of innate immunity. In neutropenic patients, infection may occur with minimal signs and symptoms and may rapidly progress to sepsis with multi-organ failure [5].

As fever may constitute the only sign in these patients, febrile neutropenia (FN) should be considered a true emergency [6,7].

Neutropenia with decreased production with marrow hypoplasia can be primary and due to chronic benign neutropenia, cyclic neutropenia, and other congenital and familial neutropenias. It can be secondary to cytotoxic drugs, aplastic anemia, leukemia, drug reactions, and infections. Neutropenia with increased destruction with marrow hyperplasia is due to hypersplenism and immune neutropenia [8].

The aim of this study was to assess the degree of adoption of management of FN in nonmalignant conditions to the implemented guidelines in Hematology Unit in Assiut University Children Hospital (AUCH).

Patients and methods

Research design: clinical retrospective study on FN in nonmalignant conditions in children at AUCH from April 1, 2018 to March 31, 2019 (IRB: 17100058).

Inclusion criteria

(1) All patients with age below 18 years.
(2) Patients with fever and complete blood count (CBC) showing neutropenia (<1500/mm^3).

Exclusion criteria

(1) Age below 18 years.
(2) Patients with normal CBC.
(3) Patients on chemotherapy.

Results

Results of this study given in Fig. 1 and 2 and Tables 1–4.

Discussion

Neutropenia is a decrease in the circulating neutrophils in the peripheral blood. Our study was performed in Assiut University Children Hospital –Hematology Unit during the period April 1, 2018 to March 31, 2019.

It included 50 patients with FN. Their ages ranged from 4 months to 14 years with mean age 9.08 ± 3.96, 22 of patients were males (44%) and 28 were females (56%).

Patients included in our study presented with neutropenia as a part of pancytopenia 100%. The most common etiology of pancytopenia in our study was due to nonmalignant causes 92%. This is in agreement with a study that reported 81.8% of cases with nonmalignant pancytopenia [9].

Regarding the causes of nonmalignant pancytopenia in our study, aplastic anemia was the most common cause 92%. This is in agreement with the study that reported that aplastic anemia was the most common cause of pancytopenia [10].

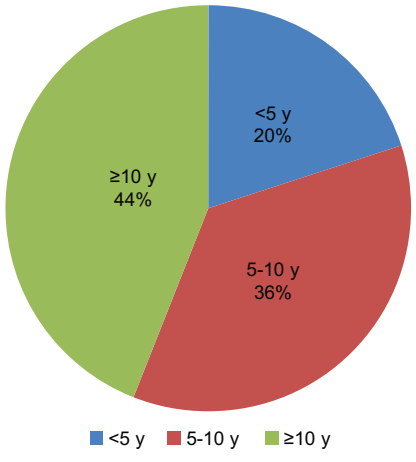
As a result of pancytopenia patients included in our study, they mostly presented with fever 100%, generalized weakness and dizziness 90%, and bleeding manifestations 36%. By examination, the most common clinical findings were raised body temperature greater than or equal to 38°c and pallor 100%. This result is in agreement with a previous study on pancytopenic patients that reported generalized weakness in 90.4%, fever in 69.04%, bleeding manifestations in 33.34%, and pallor in 100% [11].

Regarding investigations in our study, CBC was done for 100% of cases showing 12% mild neutropenia with absolute neutrophililc count (ANC) (1000–1500)/mm^3, 8% moderate neutropenia with ANC (500–1000/mm^3), and 80% severe neutropenia with ANC less than 500/mm^3, so in our study, most patients had severe neutropenia with higher risk for recurrent infections. This is in agreement with a previous study conducted in Cairo University on patients with FN and aplastic anemia, which reported that 90% of studied patients had severe neutropenia [12].

In our study, blood cultures have been done for 72% of cases, in 40%, there was no growth and was positive in 32%. Gram-negative organisms (*Escherichia coli* and *Klebsiella*) were isolated from 18%. Gram-positive organisms (*Staphylococci*) were isolated from 10% and fungal growth in 4%. Unfortunately, there was no complete data about fungal species in our study.

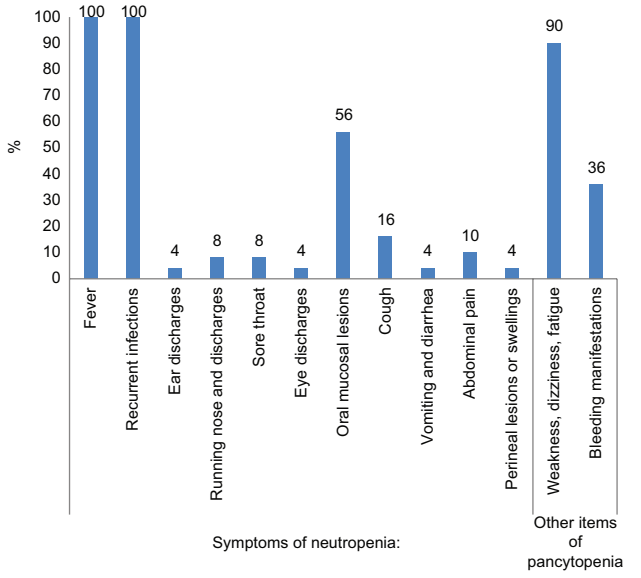
Similarly, a study reported positive blood cultures in 31.8% of cases with different results of isolation of organisms (Gram-positive cocci in 18.2%, Gram-negative bacilli in 12%, and fungal growth in 3%) [13].

Figure 1



Age distribution among studied patients (n = 50).

Figure 2



Clinical presentation of the studied patients (n = 50).

Table 1 Laboratory investigations of the studied patients (*n* = 50)

Laboratory investigation	Number (*n*=50) [*n* (%)]
CBC	
Neutropenia (ANC <1500/mm^3)	50 (100)
Mild neutropenia (1000-1500/mm^3)	6 (12)
Moderate neutropenia (500-1000/mm^3)	4 (8)
Sever neutropenia (<500/mm^3)	40 (80)
Profound neutropenia (<200/mm^3)	20 (40)
Thrombocytopenia (<150×10^9/liter)	50 (100)
PLT<20×10^9/l	18 (36)
PLT≥20×10^9/l (all<80)	32 (64)
Anemia	50 (100)
Hb<7 g/dl	30 (60)
Hb≥7 g/dl	20 (40)
CRP	
Abnormal (high CRP >30)	24 (48)
Liver function tests	
Abnormal	2 (4)
Hyperbilirubinemia and elevated enzymes	2 (4)
Blood culture	
Abnormal	16 (32)
Microbiological isolates	
1 Gram-negative organisms	9 (18)
E. coli	6 (12)
Klebsiella spp.	3 (6)
Gram-positive organisms	5 (10)
Staph aureus	5 (10)
Others	2 (4)
Fungal growth	2 (4)
Urine analysis	
Abnormal (pus cells and crystals)	5 (10)
Urine culture	
Abnormal	2 (4)
E. coli	2 (4)
Bone marrow biopsy	
Hypocellular	46 (92)

ANC, absolute neutrophililc count; CBC, complete blood count; CRP, C-reactive protein; Hb, hemoglobin; PLT, platelet.

Another study reported no growth in blood cultures of 41.5% of patients and reported isolation of nonhemolytic streptococci in 1.9%, streptococcus viridians in 1.9%, and *E. coli* in 1.9% [12].

In another previous study on neutropenic children, blood cultures were positive in 15% of cases [14].

In our study, bone marrow biopsy was done for 92% of cases, all of which were hypocellular. This is in agreement with another study in which bone marrow biopsy was done for all cases 100%, all were hypocellular [12].

Regarding imaging studies in our study, chest radiography was done for 40% of cases, 36% were normal, and in 4%, there was consolidation. Abdominal ultrasonograghy was done for 68% of our patients, nonspecific mesenteric lymphadenitis found in 4%, and typhilitis found in 2%.

Table 2 Management of studied patients (*n*=50)

Management of studied patients	Number (*n*=50) [*n* (%)]
Isolation of patients	50 (100)
Follow-up charts of vital signs	50 (100)
Medication	
Antimicrobial therapy	
Antibiotics	
Monotherapy	26 (52)
Cefepime	6 (12)
Piperacillin/Tazobactam	14 (28)
Meropenem	6 (12)
Combination therapy	24 (48)
Ceftazidime and Amikacin	18 (36)
Vancomycin and cefepime	6 (12)
Antiviral drugs (acyclovir)	15 (30)
Antifungal drugs (micafungin 'mycamine')	40 (80)
G-CSF	20 (40)
Others	
Immunosuppressive therapy (cyclosporine)	4 (8)
Androgen (Danazole)	8 (16)
Eltrombopag (revolade)	4 (8)
Blood products' transfusion	
Packed RBCs	20 (40)
Platelet-rich plasma or platelet concentrate	18 (36)
Both	18 (36)
Stay at hospital (in days)	
Mean±SD	13.46±5.32
Duration of fever (in days)	
Mean±SD	6.82±3.52

G-CSF, granulocyte colony-stimulating factor; RBC, red blood cells.

In another study, chest radiography results were available for 7.5% of cases, 5.7% were normal, while one only had increased bronchovascular markings [12].

Regarding the causes and types of infections in the neutropenic patients in our study were as follows: oral mucosal lesions 56%, fever of unknown origin 44%, anal abscess 4%, sore throat and acute tonsillitis 8%, pneumonia 4%, otitis media 4%, conjunctivitis 4%, gastroenteritis 4%, and sinusitis 4%.

Regarding isolated fever that is common in neutropenic patients, our study is similar to a previous study that reported fever of unknown origin in 49% of neutropenic patients [14].

Another study on patients with neutropenia reported similar types of infections but with different rates as follows: mucositis 33.4%, pneumonia 24.7%, tonsillitis or sinusitis 9.9%, gastroenteritis 8.6%, anal abscess 3.7%, dental abscess 1.2%, and fever of unknown origin 23% [15].

Regarding management of patients included in our study, all patients were isolated in isolation room in the Hematology Unit and follow-up charts have been done for all of them. Regarding medications,

Table 3 Types of infection in studied patients (*n*=50)

Types of infection	*n*=50 [*n* (%)]
Sore throat, acute tonsillitis	4 (8)
Sinusitis	2 (4)
Pneumonia	2 (4)
Conjunctivitis	2 (4)
Otitis media	2 (4)
Dental abscess and gum ulcers	28 (56)
Gastroenteritis	2 (4)
Anal abscess	2 (4)
Isolated fever (unknown origin)	22 (44)

Table 4 Causes of neutropenia in the studied patients (*n*=50)

Causes of neutropenia	*n*=50 [*n* (%)]
Isolated neutropenia	0
Part of pancytopenia	50 (100)
Bone marrow infiltration	4 (8)
Suspected leukemia	3 (6)
HLH	1 (2)
Aplastic anemia	46 (92)
Inherited	8 (16)
Fanconi anemia	8 (16)
Acquired	38 (76)
Drug-induced	4 (8)
NSAIDs (novalgin)	2 (4)
Methotrexate	2 (4)
Posthepatitis (hepatitis A)	4 (8)
Idiopathic	30 (60)

HLH, hemophagocytic lymphoproliferative histiocytosis.

cephalosporins were used as first-line treatment as monotherapy (cefipime 12%) and combination therapy (cefipime and ceftazidime 48%). Other drugs used as monotherapy were piperacillin–tazobactam 28% and meropenem 12%. Vancomycin was added in 12% as combination therapy.

Antiviral therapy was used in 30% and antifungal therapy in 80%.

Granulocyte colony-stimulating factor (G-CSF) was used in 40% of cases and blood products in 40%.

This is in agreement with a previous study in which cephalosporins were used as first-line drugs in 45.5% of neutropenic episodes and in ten of such episodes grading up to higher antibiotics like piperacillin, teicoplanin, and vancomycin that were required.

Antifungals (liposomal Amphotericin B and Fluconazole) were started in 21 episodes in the study, in four episodes, there was culture-proven Candidal growth, and in others, they were started either empirically for persisting fever spikes or based on clinical diagnosis of oral/esophageal/vaginal candidiasis. Granulocyte colony-stimulating factor was used in 21.6% of episodes and blood products in 40.9% [16].

Another study on neutropenic patients reported that Ceftazidime was used as empirical antibiotic in 30%, Ampicillin/Sulbactam in 43%, piperacillin–tazobactam 5.7%, meropenem 5.7% and amoxicillin–clavulinic acid 9.4%, and Vancomycin in 16.9%. Antifungal therapy was given in 17% [12].

For patients included in our study, no prophylactic antibiotics on discharge were recommended.

However, in a previous study, 38 of 40 children included in the study were on co-trimoxazole prophylaxis for more than a week [16].

The duration of fever in patients included in our study ranged from 1 to 15 days with mean 6.82 ± 3.5.

In a previous study, the median duration of fever in the episodes was 5 days [16].

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Conflicts of interest
None declared.

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