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Original Article

Pattern of Bacterial and Fungal Infections in Neutropenic Pediatric Patients

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Abstract

Backgrounds: Neutropenia can be associated with life-threatening infections. Gram negative and staphylococcal infections are the most common pathogens. The spectrum of bacterial isolates has changed considerably over the past four decades. The objective of the present study was to evaluate the pattern of bacterial and fungal infections in neutropenic pediatric patients.

Methods: A non-randomized descriptive and cross-sectional study involving 100 hospitalized children was carried out at the emergency and pediatric hematology and oncology units of hospitals affiliated to Mashhad University of Medical Sciences from September 2004 to September 2005. Neutropenic children younger than 12 years old with clinical signs of infection and/or fever were enrolled in the study.

Results: The study comprised of 100 febrile and/or infected neutropenic episodes occurring in 57 male and 43 female children younger than 12 years old with a mean age of 4.55±3.33 years. A total of 87 pathogens were cultured: 37 (42.5%) from urinary tract and 50 (57.5%) from other sites; 54 (62.1%) were gram-negative bacteria, 21 (24.1%) were gram-positive bacteria, and 12 (13.8%) were fungus. Pseudomonas aeruginosa and staphylococcus aureus were the most frequent gram-negative and gram-positive isolates respectively. Candida spp. was the only isolated fungus. Acute lymphoblastic leukemia was the most common disease encompassing 33% of all cases.

Conclusion: As the patterns of isolates in neutropenic patients are not the same in different parts of the world and gram-negative organisms were still the most common pathogens isolated in our study population, therapeutic adjustments for empirical antibiotic therapy are likely to be focused on gram-negative pathogens.

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Keywords ● Neutropenia ● fever ● infection ● children

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Introduction

Polymorphonuclear leukocytes (PMNs) are the most crucial cellular defense against invading microorganisms.[1] Cellular defense disorders related to PMNs are qualitative (functional) or quantitative (neutropenia). Neutropenia is defined as decreased total circulating neutrophils,

which varies with age and race. Absolute neutrophil count (ANC) is 1000/µl for Caucasian children between two weeks and one year of age and 1500/µl for those older than one year.[2] Neutropenia is associated with infections that may be life-threatening, particularly if not treated immediately.[1,3] Neutropenia due to cytotoxic chemotherapy is the most common risk factor for severe infections in patients with hematologic cancer.[4] Fever is the most common sign of infection and neutropenic fever is an emergency that requires prompt assessment and treatment with antibiotics.[5] The pattern of fever in neutropenia is not pathognomonic of any type of infections and can be suppressed by the antipyretic effects of drugs such as corticosteroids.[4]

The severity of neutropenia is associated with increased pyogenic infections. Mild and moderate neutropenia are defined as ANC 1000-1500/µl and 500-1000/µl respectively. Severe neutropenia with ANC less than 500/µl is associated with increased risk of pyogenic infections including perirectal infections, furuncles, pneumonia, septicemia, and also oral infections such as stomatitis, gingivitis, and periodontitis.[2] Most of severe infections are observed when ANC drops to < 100 cells/µl.[6]

The spectrum of bacterial isolates has changed considerably over the past four decades.[6] European Organization for Research and Treatment of Cancer (EORTC) has shown that the pattern of microorganisms isolated changes almost every 2-3 years. Therefore, it is suggested to study the pattern of infections and causative organisms at an interval of 2-3 years.[7]

Hence, regarding this changing pattern of bacterial pathogens, the objective of the present study was to evaluate the pattern of bacterial and fungal infections in neutropenic pediatric patients in east of Iran via isolating and identifying the pathogenic organisms.

Subjects and Methods

Study design

A non-randomized descriptive and cross-sectional study involving 100 hospitalized children was carried out at the emergency and pediatric hematology and oncology units of Quaem, Imam Reza, and Dr. Sheikh Hospitals affiliated to Mashhad University of Medical Sciences from September 2004 to September 2005. Neutropenic children younger than 12 years old with clinical signs of infection and/or fever were enrolled in the present study. Chemotherapy induced neutropenic children who developed fever within 24 hours after administration of chemotherapy and the fever subsided within next 24 hours after completion of chemotherapy,[8] and also children with fever occurring during or within 6 hours after transfusion of blood, blood products, and other intravenous fluids,[8] were excluded from the study.

Definitions

Neutropenia was defined as median ANC less than 1500/µl;[9] with mild neutropenia as ANC of 1000-1500/µl, moderate as ANC of 500-1000/µl, and severe as ANC less than 500/µl.[2]

Infection was defined as at least one of the following conditions: fever (>38 °C), systolic blood pressure <60 mmHg, or signs of localized infection (inflammation) in a major organ/system.[9]

Fever was defined as a single oral temperature of 38.3°C or a persistent fever (temperature reading of 38°C on at least three consecutive evaluations, at > 4-hour intervals) within 24 hours period, which was not associated with an obvious non-infectious cause.[8]

Collection of Clinical Data

All participating units were required to report all eligible cases met the inclusion criteria to the data centre. All eligible recruited patients underwent a thorough assessment including detailed history, careful and complete physical examination, and relevant hematological, microbiological, and radiological investigations.

Collection of Clinical Specimens

Three ml blood was collected in dipotassium salt of ethylene diamine tetra-acetic acid (K_2 EDTA) within two hours for complete blood count. Two sets of 2 ml blood were collected at one-hour interval for blood culture. Throat swabs for culture were sent to the laboratory within 2 hours.

Pus swabs, pus, and exudates from skin, mouth, ear, eyes, joint, sinuses, wound and ulcers with sterile disposable syringes or sterile cotton wool swabs were delivered to the laboratory within 2 hours. Mid stream urine samples were collected and delivered to the laboratory for urine culture.

One to two ml of stool specimens were collected and transmitted quickly to the laboratory for stool examination and stool culture.

Effusion (peritoneal, pleural etc.) fluids were aspirated and transported to the laboratory within 2 hours for routine examination and culture.

Cerebrospinal fluid samples were collected with sterile disposable syringes and transported to the laboratory within 1 hour after collection for routine examination and culture.

Statistical Analysis

SPSS software version 12 was used for data management. The bivariate correlations procedure was used to compute Pearson's correlation coefficient. A P value 0.05 was considered as statistically significant.

Results

Patient Characteristics

During the study period, 100 neutropenic episodes that occurred in 100 pediatric patients were studied. Demographic and history profiles of the patients are presented in table 1.

Table 1: Demographic and history profile of patients.

Mean age	n
Mean age=4.55±3.33 years	
Mean age for male=4.43±3.08 years	
Mean age for female=4.70±3.67 years	
Age group	
2-12 months	17
21-24 months	13
2-5 years	28
5-12 years	42
Gender	
Male	57
Female	43
Underlying disease	
ALL	33
Aplastic anemia	17
Viral infection	10
Lymphoma	8
AML	7
Histiocytosis	7
Kala Azar	5
Septicemia	5
Thalassemia	4
Megaloblastic anemia	2
Familial neutropenia	1
SCA	1
Total	100

n: Number of patients, ALL: Acute lymphoblastic leukemia, AML: Acute myelogenous leukemia, SCA: Sickle cell anemia

White Blood Cell Counts

The mean absolute white blood cell count at the time of diagnosis was 3368±2940/µl (range 100-12500/µl). It was categorized into four groups: <1000/µl (20%), 1000-2000/µl (24%), 2000-4000/µl (34%), and >4000/µl (22%). The mean absolute neutrophil count was 643±407/µl (range 0-1400/µl), categorized according to neutropenia severity into three groups: <500/µl (severe neutropenia, 38%), 500-1000/µl (moderate neutropenia, 40%), and >1000/µl (mild neutropenia, 22%).

Severe neutropenia was most detected in 5-12 years (47.4%) and 2-5 years (31.6%) old groups. Moderate neutropenia was most detected in 5-12 years old group (55%). There was a statistically significant difference in the severity of neutropenia according to the age group (r=-0.235, P=0.007). Severe and mild neutropenia were most detected in males (65.8% *v* 34.2% and 63.6% *v* 36.4% respectively). There was no statistically significant difference in the severity of neutropenia according to gender(r=0.060, P=0.526).

Severe neutropenia in acute lymphoblastic leukemia (ALL, 50%), moderate neutropenia in ALL (30%) and aplastic anemia (12.5%), and mild neutropenia in histiocytosis (22.7%) were most detected. There was a statistically significant difference in the severity of neutropenia according to the underlying disease(r=0.366, P<0.001). These associations between mean ANC and age group, gender, and underlying diseases are shown in table 2.

Impact of Age, Gender and Underlying Disease on PMN Count

The independent variables, age, gender, and underlying disease were regressed onto the dependent variable, PMN count (r=0.528, P <0.001). Linear regression found a statistically significant effect [relative risk (RR) =-0.062, 95% confidence interval (CI) (-0.101 to -0.023), P=0.002] of age on PMN count. Underlying disease was a statistically significant predictor of PMN count [RR=-0.120, 95% CI (0.074 to 0.166), P <0.001]; but gender was not [RR=-0.107, 95% CI (-0.157 to 0.371), P = 0.423].

Microbiology

Total 87 micro-organisms, 37 (42.5%) from urine and 50 (57.5%) from other sites were isolated. Of them 21 (24.1%) were gram-positive cocci, 54 (62.1%) were gram-negative rods, and 12 (13.8%) were fungal organisms. Sources of infection and isolated pathogens in neutropenic patients are listed in table 3.

Sources of Infection

Bloodstream infection occurred in 12% of cases. When a localized infection was present, the most frequent site was the urinary tract (37%), followed by skin (17%), bowel (10%), joint (5%), mouth (4%), and eye (2%). In 13% of cases, no organism or source of infection was found.

Isolated Pathogens

Pseudomonas aeruginosa was the most frequently isolated pathogens (20.7%), followed by staphylococcus aureus (18.4%), Escherichia coli (16.1%), Klebsiella spp. (14.9%), Candida spp. (13.8%) and Salmonella spp. (5.7%). Staphylococcus epidermidis, Streptococcus pneumoniae, Shigella spp., and Proteus spp. accounted for 2.3% of pathogens each. The other isolated pathogen was coagulase negative staphylococcus (1.1%). S. aureus was the

Table 2: Mean absolute neutrophil count in various age groups, sexes, and underlying diseases.

	Mean ANC (643±407/µl)						Total	P-value
	<500/µl		500-1000/µl		>1000/µl			
Age group	n	%	n	%	n	%		
2-12 months	3	7.9	7	17.5	7	31.8	17	
21-24 months	5	13.1	3	7.5	5	22.7	13	
2-5 years	12	31.6	8	20	8	36.4	28	
5-12 years	18	47.4	22	55	2	9.1	42	0.002
Gender								
Male	25	65.8	18	45	14	63.6	57	
Female	13	34.2	22	55	8	36.4	43	NS
Underlying disease								
ALL	19	50	12	30	2	9.1	33	
Aplastic anemia	9	23.7	5	12.5	3	13.6	17	
Viral infection	3	7.9	4	10	3	13.6	10	
Lymphoma	2	5.3	4	10	2	9.1	8	
AML	3	7.9	4	10			7	
Histiocytosis			2	5	5	22.7	7	
Kala Azar	2	5.3	3	7.5			5	
Septicemia			2	5	3	13.6	5	
Thalassemia			4	10			4	
Megaloblastic anemia					2	9.1	2	
Familial neutropenia					1	4.5	1	
SCA					1	4.5	1	<0.001
Total	38	100	40	100	22	100	100	

ANC: Absolute neutrophil count, n: number of patients, ALL: Acute lymphoblastic leukemia, AML: Acute myelogenous leukemia, SCA: Sickle cell anemia, NS: Non-significant

Table 3: Sources of infection and isolated pathogens in neutropenic patients**.**

	Urinary tract (N=37)	Skin (N=17)	Blood (N=12)	Bowel (N=10)	Joint (N=5)	Mouth (N=4)	Eye (N=2)	Unknown (N=13)
Gram-positive (n=21)								
Staff epidermidis	2 (5.4)							
Staff aureus		3 (17.6)	8 (66.7)		5 (100)			
Streptococcus pneumoniae						2 (50)		
Staff coagulase negative						1 (25)		
Gram-negative (n=54)								
Escherichia coli	12 (32.4)			2 (20)				
Klebsiella spp.	6 (16.2)	3 (17.6)	2 (16.7)				2 (100)	
Pseudomonas aeruginosa	5 (13.5)	11 (64.7)	2 (16.7)					
Salmonella spp.				5 (50)				
Shiegella spp.				2 (20)				
Proteus spp.	2 (5.4)							
Fungi (n=12)								
Candida spp.	10 (27)			1 (10)		1 (25)		
No culture								13

N: number of patients. Values within parentheses indicate percentage (%), spp., species

most frequently isolated gram-positive cocci (76.2%), followed by S. epidermidis and S. pneumoniae (9.5%), and coagulase negative Staphylococcus (4.8%). P. aeruginosa was the most frequently isolated gram-negative rods (33.3%), followed by E. coli (25.9%), Klebsiella spp. (24%), Salmonella spp. (9.2%), Shigella spp. and Proteus spp. (3.7%).

Sources of Infection and Isolated Pathogens

E. coli was the most frequently isolated pathogen from urinary tract (32.4%), followed by Candida spp. (27%), Klebsiella spp. (16.2%), and P. aeruginosa (13.5%). P. aeruginosa was the most frequently isolated pathogen from skin (64.7%). S. aureus was the most frequently isolated pathogen from blood (66.7%). Salmonella spp. was the most frequently isolated pathogen from bowel (50%). S. aureus was the only isolated pathogen from joint (100%). S. pneumoniae was the most frequently isolated pathogen from mouth (50%). Klebsiella spp. was the only isolated pathogen from eye (100%; table 3).

The Relation of Severity of Neutropenia and Isolated Pathogens

In severe neutropenia, the most frequently isolated micro-organisms were S. aureus (23.7%), P. aeruginosa, and Candida spp. (15.8%). In moderate neutropenia, the most frequently isolated micro-organisms was P. aeruginosa (27.5%). In mild neutropenia, the most frequently isolated micro-organisms were E.coli (31.8%) and Klebsiella spp. (27.3%). There was no statistically significant difference

in the distribution of isolated pathogens according to the severity of neutropenia (P=0.215).

Discussion

Bacterial infections have been reported to account for life-threatening complications in 5-10% of febrile episodes in childhood malignancies.[10,11]

In the current study, the mean absolute white blood cell count at the time of diagnosis was 3368±2940/µl, and the mean ANC was 643±407/µl, while Viscoli et al.[9] have reported the median absolute white blood cell count of 250/µl and the median ANC of 18/µl. This difference is likely to be due to that Viscoli et al. study was conducted on pediatric patients with cancer who were receiving chemotherapy, whereas our study has focused on neutropenic pediatric patients and not necessarily on patients with cancer.

Patients with severe neutropenia (ANC<100) had slightly higher incidence of documented infection (57%),[12] and there was no difference in the rates of infection when ANC was < 200 compared with a higher ANC.[13] In our study, 38% of infections occurred in the severe neutropenic group (ANC<500). This would suggest that there is no significant association between severity of neutropenia and the incidence of infection.

We observed severe neutropenia in ALL (50%), moderate neutropenia in ALL (30%) and aplastic anemia (12.5%), and mild neutropenia in histiocytosis (22.7%). These findings exhibit the strongest association between severity of neutropenia and the underlying disease.

In the current study, 87% of neutropenic episodes had established infection and in 13% of cases no pathogen was cultured. Roguin et al.[12] have reported that infection was certain in 36% of febrile episodes, probable in 14%, and not determined in 50%. However, Hodgson-Viden et al.[14] have demonstrated 21.4% and 78.6% positive and negative cultures, respectively. This significant difference may be due to different sampling methods and laboratory procedures.

Our results show that among 87 cases, urinary tract (42.5%), skin (19.5%), blood (13.8%), bowel (11.5%), joint (5.7%), mouth (4.6%), and eye (2.3%) were the most frequent sources for infection. Mutnick et al.[15] have shown that the most frequently isolated pathogens of 2042 isolates were from blood-stream, respiratory, urinary, and cutaneous infection sites in 33 oncology centers, clinics, and hospitals in North America. Also, Roguin et al.[12] demonstrated that blood (14.1%), mouth (7.4%), throat (7.4%), lungs (6.7%), and skin (6.7%) were the most frequent sites of localized infection. Jones et al.[13] indicated that infections occurred in 38% of the patients and blood cultures were positive in 58% of documented infections. As suggested by other investigators, bloodstream infections in patients with cancer are mainly considered to be complications of neutropenia.[16] In the present study, bloodstream infection was detected in 13.8% of the episodes, predominantly caused by gram-positive organisms (66.7%). Almost similar results have been documented by Mahmud et al.[8] Naqvi et al.[17] Burney et al.[18] and Fleischhacka et al.[19] Currently, in all trials performed by International Antimicrobial Therapy Cooperative Group (IATCG) of EORTC,[20] gram-positive micro-organisms have been isolated in approximately 15% of episodes and caused approximately 60% of bloodstream infections.[21] Maldini et al. have reported that the most frequent isolate from blood was coagulase negative staphylococcus (32.2%).[22] However, our study demonstrated that S. aureus was the most frequently isolated pathogen from blood (66.7%).

Gram-negative bacilli were the most common cause of infection in the neutropenic patients since the late 1960s until early 1980s.[23] Schimpff et al.[24] have shown that gram-negative bacilli were cultured in approximately 60-80% of infections, of which P. aeruginosa was the most important isolate. In the mid 1980s, the spectrum of isolated pathogens began to change. Gram-positive cocci have taken the place of gram-negative bacilli, constituting 50-70% of bacteremias with single organisms.[8] This has been confirmed by the results of the eight therapeutic trials performed by the IATCG-EORTC in the last 22 years in febrile and neutropenic patients.[19] Coagulase negative staphylococcus and S. aureus were the predominant organisms. This change from gram-negative to gram-positive pathogens is probably multifactorial. These novel observations may be explained by aggressive chemotherapeutic regimens that cause more severe mucositis, longer durations of neutropenia, almost uniform use of long-dwelling right-atrial catheters, use of H_2-receptor antagonists and use of prophylactic antibacterial agents with relatively weak coverage of gram-positive organisms.[25] In addition to this change from gram-negative to gram-positive organisms, new gram-positive isolates have become important etiologies of infection.[26] In the present study, 62.1% of the isolates were gram-negative and 24.1% were gram-positive. S. aureus was the commonest gram-positive isolate whereas the most common gram-negative isolates were P. aeruginosa followed by E. coli

and Klebsiella spp. Similarly, Burney et al.[18] have reported that 54% of organisms were gram-negative and 46% were gram-positive. E. coli, P. aeruginosa, S. aureus, Enterococcus spp., and Streptococci were the commonly isolated organisms. However, Mutnick et al.[15] have documented S. aureus, E. coli, coagulase negative Staphylococcus, Enterococcus spp., and Klebsiella spp. Mahmud et al.[8] have shown S. aureus, E. coli, Klebsiella spp. and P. aeruginosa; and Roguin et al.[12] have demonstrated that Staphylococci (both coagulase-negative and coagulase-positive strains) and P. aeruginosa were the organisms most frequently isolated. These findings are not consistent with our results and depict that the pattern of isolates in neutropenic patients are not the same in different parts of the world.[18]

Currently, the two most common invasive fungal infections in neutropenic pediatric patients are caused by Candida spp. and Aspergillus spp.[27] Similarly, our data showed that 13.8% of the isolates were Candida spp.

Conclusions

The results of the present study revealed that the pattern of isolates in neutropenic patients were not the same with other parts of the world and gram-negative organisms were still the most common pathogens isolated in our units. Hence, therapeutic adjustments for empirical antibiotic therapy are likely to be focused on gram-negative pathogens. Also, a quality infection control policy with a close and strict clinical and microbiological surveillance system aiming at early detection of infections remains the standard of care in neutropenic pediatric patients.

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Conflict of Interest: None declared

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