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Özgün Araştırma / *Research Article*

Risk Factors for Invasive Bacterial Infection and Mortality in Febrile Neutropenic Children

Febril Nötropenik Çocuk Hastalarda Gelişen İnvazif Bakteriyel Enfeksiyon ve Buna Bağlı Gelişen Mortalitede Risk Faktörleri

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ABSTRACT

Objective: *Febrile neutropenia (FN) is a common and life-threatening complication that develops during therapy for childhood cancer. Serious bacterial illness is a significant cause of morbidity and mortality for neutropenic patients The primary objective of the study was to determine etiology and clinical course of fever in neutropenic children with cancer. The aim was to identify the risk of development of invasive bacterial infection (IBI) and factors associated with mortality in pediatric cancer FEN patients.*
Method: *This study was conducted in University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital between January 2006 and and December 2013. Invasive bacterial infections and related mortality in children aged 0 to 18 years of age were documented.*
Results: *A total of 325 neutropenic febrile episodes of 134 patients were evaluated. The most common preexisting risk factor for invasive bacterial infection was acute myeloid leukemia phenotyp. Other risk factors included, thrombocytopenia, bloodstream infection, C-reactive protein value >9 mg/dL and pneumoniae. In our case series overall infection- associated mortality was found as 4% similar as in the literature.*
Conclusion: *Invasive bacterial infections is still be major cause of mortality and morbidity for pediatric leukemia.*

Keywords: *Invasive bacterial infection, child, leukemia, risk factor*

ÖZ

Amaç: *Çocukluk çağı kanserlerinde tedavi sırasında gelişen febril nötropeni sık görülen ve yaşamı tehdit eden bir komplikasyondur. Ciddi bakteriyel enfeksiyonlar nötropenik olan hastalarda mortalite ve morbidite nedeni olmaktadır. Çalışmanın amacı çocukluk çağı lösemilerinde gelişen febril nötropenilerde invazif bakteriyel enfeksiyon gelişme riskini belirlemek ve mortalite ile ilişkili durumları ortaya koymaktır.*
Yöntem: *Çalışma, retrospektif olarak Ocak 2006-Ekim 2013 tarihleri arasında, Sağlık Bakanlığı Sağlık Bilimleri Üniversitesi Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim Araştırma Hastanesinde yürütülmüştür. 0-18 yaş çocuk lösemi hastalarında gelişen invazif bakteriyel enfeksiyonlar ve buna bağlı gelişen mortalite dökümante edilmiştir.*
Bulgular: *Çalışmada, 134 hastanın 325 febril nötropeni atağı incelenmiştir. İnvazif bakteriyel enfeksiyon gelişmi için en yüksek risk faktörü akut miyeloid lösemi fenotipi olarak bulunmuştur. Diğer risk faktörleri ise trombositopeni, kan dolaşım enfeksiyonu, C-reaktif protein >9 mg/dL ve pnömoni olarak bulunmuştur. Olgu serimizde enfeksiyon ilişkili mortalite %4 olarak bulunmuştur, bu da literatürle benzer düzeydedir.*
Sonuç: *İnvazif bakteriyel enfeksiyonlar pediatirk lösemilerde halen önemli bir mortalite ve morbidite nedenidir.*

Anahtar kelimeler: *İnvazif bakteriyel enfeksiyon, çocuk, lösemi, risk faktör*

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INTRODUCTION

Febrile neutropenia (FN) is a common and life-threatening complication of therapy for childhood cancer. Although fever in healthy individuals does not always necessarily indicate severe illness, fever in patients with neutropenia may herald a life-threatening infection. Serious bacterial infection is a significant cause of morbidity and mortality for neutropenic patients. A large proportion of the evidence of risk stratifications has been adapted from adult malignancy patients [1,2].

Survival rates among children with cancer have progressively increased in the past decades now exceeding 75 percent. However aggressive treatment of cancer has resulted in a higher risk of infection [3]. Granulocytopenia is to be considered the main risk factor for infection. Frequently, fever is the first and the only sign that indicates the presence of infection in these children and therefore, must be considered as an indication of emergency intervention [4].

Current knowledge indicates that children with cancer do not all have the same risk for invasive bacterial infection (IBI). According to Infectious Diseases Society of America, high-risk patients are those with anticipated prolonged (>7 days) and profound neutropenia (absolute neutrophil count ≤100 cells/mm^3 following cytotoxic chemotherapy) and/or significant medical comorbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes [5].

This study was conducted to describe the etiology and clinical course of fever in neutropenic children with leukemia. The aim was to identify the risk of invasive bacterial infection and factors associated with mortality in FN patients with pediatric leukemia.

METHODOLOGY

Patients

All children ≤18 years of age with cancer, fever and neutropenia (absolute neutrophil count (ANC) ≤1500/mm^3), admitted to a referral center in the Central Anatolia, Ankara Children Hematology & Oncology Education and Research Hospital, between January 1, 2006 and December 31, 2013 were evaluated.

A data sheet for evaluating each episode has been filled out including: (1) patient's age, sex, type of leukemia, underlying disease and disease stage, chemotherapy regimen of patient (initial or maintenance), (2) presence of any intravenous device, day of catheterization, (3) clinical assessment, highest axillary temperature on the first day of admission, blood pressure and signs and symptoms indicative of any clinically identifiable infectious focus (eg. presence of hypotension, fever over 39°C, paleness, etc.) (4) laboratory test results; hemoglobin level, platelet count, ANC, absolute monocyte count (AMC), quantitative serum C reactive protein (CRP (5) antifungal treatment in the last 6 months, steroid treatment in last 2 weeks (6) catheterization and peripheric blood culture results, chest X ray and thorax tomography findings and clinical infection were noted.

Clinical infection category included; upper respiratory tract infection or oral cavity infection, pneumonia, urinary tract infection, soft tissue infection, typhlitis, central nervous system infection, catheter-related bloodstream infection (CRBSI), bloodstream infection, diarrhea, sepsis and other infections.

Definitions

Febrile neutropenia was defined as a single body temperature of >38.5°C or two repeated readings of >38.0°C with neutropenia defined as ≤1500 neutrophils/mm^3. Moderate neutropenia was defined as 500-1000 neutrophils/mm^3, severe neutropenia as ≤500 neutrophils/mm^3 [5].

A child was considered to have invasive bacterial infection (IBI) if bacteremia was detected and/or a positive result of bacterial culture of specimen was obtained from a usually sterile site (e.g., indwelling catheter, urine, CSF), in the absence of a positive culture result if clinical and laboratory findings were strongly suggestive of a sepsis syndrome and/or focal organ involvement in a child with hemodynamic instability and severe malaise [6].

Diagnosis of CRBSI is based on the following: The

presence of a central venous catheter (CVC); signs of catheter insertion site infection, clinical symptoms and signs of bacteremia; resolution of the symptoms and signs of bacteremia after removal of the suspect CVC; positive blood culture; and growth of the same organism in the sample obtained from the catheter [7].

Statistical Analysis

Comparisons of the proportion of risk factors between groups were performed using a *chi*-square test. Comparisons of medians between groups were performed using the Mann-Whitney U test. A multivariate logistic regression analysis was used for assessment of association between significant risk factors for the occurrence of infection or mortality. Statistical significance was assigned to two-sided p values less than 0.5.

Ethical issues

The study was started after approval of the ethics committee of the hospital was obtained.

RESULTS

Patients' characterics

During the 7-years of study period, a total of 324 FN episodes in 134 patients (57 girls, 77 boys) were evaluated. The mean age of the patients at the time of enrollment was 6.6±4.5 years (range; 6 months-18 years). The number and percentage of children with specific cancer types and hematologic diseases were as follows; 105 (78.3%) had acute lmphocytic leukemia (ALL), 23 (17.1%) had acute myeloid leukemia (AML) and 6 (4.47%) had hemophagocytic lymphohistiocytosis. Fifty-six (17.3%) episodes were cases of relapse leukemia. None of the children had received a bone marrow transplant (Table 1).

The patients received induction chemotherapy in 247 (76.2%) episodes. During 152 FN episodes (46.9%), patients had history of indwelling intravenous catheter for a median duration of 61.5 days (1-767 days). Overall admission characteristics of 324 febrile neutropenia episodes are shown in Table 1.

The mean ANC at the enrollment was 236±334 neutrophils/mm^3. A total of 273 (84.3%) episodes of severe neutropenia (ANC <500 neutrophils/mm^3) were detected, ANC was ≤ 100 neutrophils mm^3 in 185 (57.1%), and 500-1000 neutrophils/mm^3 in 37 (11.4%) episodes.

Clinical source of infection was identified in 235 episodes (72.2%). Upper respiratory tract infection/

Table 1. Overall admission characteristics of 324 episodes of febrile neutropenia admission characteristics.

Episodes (n=324)	Numbers
Mean age in years	6.6±4.5 years
Male (%)	77 (57.4%)
Type of cancer (%)	
Acute lymphoid leukemia	105 (78.3%)
Acute myeloid leukemia	23 (17.1%)
Haemophagocytic lymphohystiositosis	6 (4.47%)
Leukemia relapse	56 (17.3%)
Use of central venous catheter (%)	152 (46.9%)
Median temperature (°C)	38,3 °C (range; 37.7 °C-40.5 °C)
Mean duration between chemotherapy initiation date and fever	184 days (range 0-1097 days)
Mean duration between last chemotherapy day and first day of febril neutropenic episod	6.8±7.35 days (range 0-49 days).

Table 2. Laboratory parameters at admission.

Parameter	Median (Range)
Hemoglobin (g/dl)	9.25 (5.2-14.7)
Platelets (/mm^3)	53500 (900-1302000)
ANC (/mm^3)	100 (0-1500)
AMC (/mm^3)	0 (0-1200)
CRP (mg/dL)	3.68 (0.01-68)

ANC: absolute neutrophile count, AMC: Absolute monocyte count, CRP: C-reactive protein.

Table 3. The number and percentage of source of clinical infection in febrile neutropenic episodes.

Etiology	Number of episodes (%)
Unidentified	89 (27.5%)
Upper respiratory tract infection/oral cavity infection	78 (24.1%)
Pneumonia	53 (16.4%)
Gastrointestinal system infection	26 (8.0%)
Central venous catheter infection	11 (3.4%)
Blood stream infection	11 (3.4%)
Urinary tract infection	13 (4.0%)
Typhylitis	4 (1.2%)
Soft tissue infection	18 (5.4%)
Other	21 (6.5%)

oral cavity infection was the most common source of infection and present in 23.1% of the patients and pneumoniae was detected in 15.1% of all episodes. The rest of the etiologies are presented in Table 3,4.

In 38 (11.7%) episodes, a pathogenic microorganism was identified from peripheral vein blood cultures. The most common microorganism identified from peripheral vein blood cultures were coagulase-negative *Staphylococcus spp.* and *Streptococcus spp.* Fungal pathogen was identified in peripheral blood cultures in 5 (1.5%) episodes (*Candida crusei* in 1, *Candida albicans* in 3, *Candida spp* in 1 episode).

Central venous catheter was present in 152 (46.9%) episodes. In 38 (11.7%) of all episodes, a pathogenic microorganism was identified in CVC and diagnosed as catheter-related bloodstream infection (CRBSI) in 13 (4%), while the remaining 25 episodes was considered as bacterial colonisation. The rate of CRBSI in catheterized patients was found as 8.5%. The pathogenic microorganisms identified were as follows in CRBSI; in 4 case (30.7%) non-albicans candida spp (2 *Candida crusei*, 1 *Candida tropicalis*, 1 unknown), in 4 (30.7%) coagulase-negative *Staphylococcus*, in 2 (15.3%) *Candida albicans*, in 2 (15.3%) *Klebsiella spp* and in 1 (7.6%) *Streptococcus pneumoniae*.

S. Pneumoniae was present in 53 (16.4%) episodes. 7 (13.2%) of 53 patients with pneumonia died. Possible IAP had been identified in 2 of 7 fatal pneumonia episodes. Most of the pneumonia infection was observed in patients recieving maintenance chemotherapy (n=30, 56.6%, p=0.002) and in 16 (30.1%) patients recurrent/progressive pneumonia was detected. The remaining 6 episodes of pneumonia were observed in patients at the admission of hospital before initiating any chemotheraphy regimen at the enrollment phase of leukemic patients.

Pathogenic microorganisms that were detected in bloodstream infections were as follows; *Candida* spp in 2, *Streptococcus* spp in 2, *Pseudomonas aeuriginosa* in 1, coagulase-negative *Staphylococcus* in 2, Klebsiella spp in 1 episode. The patient with *Pseudomonas aeuriginosa*-related bloodstream infection had died.

Invasive bacterial infection was detected in 138 (44.8%) of total of 324 episodes. Invasive bacterial

Table 4. Bacterial species recovered for 324 episodes of febrile neutropenic children, according to the site of the isolate.

Isolate	Blood	Catheter	Urine
Coagulase-negative Staphylococcus spp	18	20	
Klebsiella species	4	4	
Escherichia coli	1	3	2
Streptococcus species	7	5	
Acinetobacter species	2	1	
Enterococcus species	1	2	
Pseudomonas species	2	2	
Enterobacter cloaca	2	1	
Stap hominis	1	-	
Total	38	38	

Table 5. General description of the 13 children who died during the febrile neutropenic episode.

No	Age	Gender	Cancer type	ANC	Therapy	Clinic infection	Microorganism/source
1	2	F	ALL/remision	440	Maintenance	Pneumonia	None
2	13	M	MDS/relaps	500	İntensive	Pneumonia	None
3	15	M	AML/relaps	0	İntensive	Pneumonia	None
4	15	F	MDS/relaps	0	Intensive	Pneumonia	None
5	1,5	E	HLH/relaps	0	İntensive	Pneumonia	None
6	1	E	HLH/relaps	0	İntensive	Pneumonia	*Pseudomonas spp*
7	3	E	AML/relaps	500	İntensive	Pneumonia	None
8	10,5	F	AML/relaps	500	İntensive	CRBSI	*Klebsiella spp*
9	18	M	AML/relaps	0	İntensive	Bloodstream inf.	*Pseudomonas spp*
10	5	M	ALL/relaps	0	İntensive	Bloodstream inf.	*Candida albicans*
11	2	M	ALL/relaps	0	İntensive	Bloodstream inf	*Klebsiella spp*
12	11.5	F	ALL/relaps	0	İntensive	Bloodstream inf	*Klebsiella spp*
13	1	M	ALL/relaps	0	İntensive	URTI/Oral cavity infection	*Coagulase negative staphylococcus spp*

F: Female, M: Male, ANC: absolute neutrophil count, ALL: acute lmphocytic leukemia, AML: Acute myeloid leukemia, MDS: myelodysplastic syndrome, HLH: Hemophagocytic lymphohistiocytosis, CRBSI: catheter related bloodstream infections, URTI: urinary tract infectionb

infection was more frequently observed in AML patients (p=0.024). Thrombocytopenia (mean platelet 70494±68832/mm^3) was more frequently detected in invasive bacterial infection group (p=0.034). Invasive bacterial infection was higher in CRP >9 mg/dL group (p=0.03).

Mortality was observed in 13 (9.7%) of 134 patients and 4% in 324 febrile neutropenic episodes. In leukemia group, mortality rate was higher in AML patients compared to ALL (p<0.001).

Clinical diagnoses of fatal patients were as following; pneumonia was detected in 7 (53.8%), bloodstream infection in 3 (23%), catheter-related bloodstream infection in 1 (7.69%), gastrointestinal system infection in 1 (7.69%), oral cavity infection in 1 (7.69%) patient. Mean age of the children who died was 7.57±6.3 (range 1-18 years) years, 8 of 14 patients were male. Relevant demographic, clinical, and laboratory findings for these 13 children are described in Table 5.

Overall infection-associated mortality is found as 4%. In our cases, early clinical and laboratory factors significantly associated with death were presence of leukemia type of AML (p=0.01) and invasive bacterial infection (p=0.038). Mortality was higher in patients with pneumonia and bloodstream infection (p=0.002).

DISCUSSION

We present a series of 324 of FN episodes with an overall infection-associated mortality of 4%. In our cases, early clinical and laboratory factors significantly associated with death were presence of AML and invasive bacterial infections.

Early reports on the epidemiology of bacterial infections showed gram-negative pathogens as the major cause of infection in neutropenic children and adults. *Escherichia coli, P. aeruginosa*, and *Klebsiella* spp. were the most commonly isolated pathogens [8]. Subsequently, toward the end of the 1980s, gram-positive pathogens were being increasingly recognized as an important source of FN [9]. This shift in pathogens could be due to increased use of central venous catheters, increased prevalence of mucositis, prophylactic regimens with predominantly gram-negative activity and increases in mucositis- specific pathogens such as *viridans streptococci* [10]. The most common species identified in children with high risk febrile neutropenia and sepsis are *E. coli, S. aureus*, and *P. aeruginosa* concordant with our results [6].

Catheter-related bloodstream infection is the most common complication of catheterization . Hakim et al. [11] investigated 337 FN episodes in children and in 86(25%) episodes they had demonstrated infection and probable infection was detected in 75 episodes (22%). The most frequently isolated organisms were determined as viridans streptococci [13], *Pseudomonas* spp (6) and *E. coli* (6) Afzal et al. [12] studied 425 pediatric ALL patients and the most common organisms identified were coagulase negative *Staphylococcus* (11/85, 12.9%), viridans group *Streptococcus* (11/85, 12.9%), *Staphylococcus aureus* (10/85, 11.8%). We detected coagulase negative *Staphylococcus* commonly in catheter and blood cultures (4 in 13 CRBSI) similar to Afzal et al. But in our cohort candida species were the most common microorganism (6 in 13 CRBSI). The mean of catheter day in candida species associated CRBSI detected patients was 111.4 days (21-194 days). The mean duration of catheterization in all CRBSI positive patients was 65.9 days (2-194 days). Increase in catheter dwell time could be associated with candida related infection in our patients. All of our patients were severely neutropenic and had hematologic malignancy and also increase in catheter dwell time was observed in our patients [13].

In our study pneumonia was detected in 53 (16.4%) episodes. Seven (13.2%) patients with pneumonia died in our case series. Tezcan et al. [14] evaluated 621 episodes of febrile neutropenia in pediatric patients and detected 425 infections in 345 episodes. They found that pneumonia was the most common infection (90/425; 32.7%).

We especially evaluated invasive bacterial infection and risk factors for developing IBI in febrile neutropenic patients. According to our study AML phenotype, thrombocytopenia, bloodstream infection, and pneumonia was associated with IBI. Because mortality was observed in only IBI patient in our case

series. Santolaya et al. [6] investigated risk factor for IBI and febrile neutropenia. They had observed CRP, hypotension, relapse of leukemia, lower platelet counts and recent receipt of chemotherapy. They suggested that identification of these 5 risk factors during the first 24 h of hospitalization was helpful in discriminating between children with a high or low risk for invasive bacterial infection (IBI). We did not find any statistical relation between IBI and chemotherapy regimen, or time interval between chemotherapy and FN episodes.

When microbiologically or clinically documented infections experienced by pediatric patients with FEN were investigated, documented infection is less commonly observed in children compared to adults with a frequency of 40–50% [18]. We identified bacterial and fungal microorganisms in only 20 (14.4%) invasive bacterial infection positive episodes. Bacterial isolation technique using conventional microbiologic techniques have rarely identified microbial agents in more than 25% of children with clinical signs and laboratory findings, suggesting a high risk for an invasive bacterial infection [6]. We found mortality rate in our patients as 4%. All deceased patients were at high risk for invasive bacterial infections. Mortality associated with febrile neutropenia in cancer patients ranges from 2-6% in children [16,17]. Santolaya et al. [18] investigated clinical and laboratory factors associated with death in children with cancer and febrile neutropenic episodes. They found factors significantly associated with death as relapse of ALL, hypotension, diagnosis of sepsis, ANC 100/mm^3, AMC 100/mm^3, BUN 18 mg/dL, CRP 90 mg/L, and positive cultures. They found the most common pathogens as *E. coli, S. aureus, P. aeruginosa* and *Klebsiella species*. Two longitudinal studies performed by the University Health System Consortium in the United States provided information for both adult and pediatric populations. The most important independent risk factors for death were presence of an invasive fungal infection, Gram-negative or Gram-positive bacteremia, pneumonia, and/or comorbidity factors [19]. In our cases, early clinical and laboratory factors significantly associated with mortality were presence of AML (p=0.01) and presence of invasive bacterial infection (p=0.038). Mortality was higher in patients with pneumonia and bloodstream infection (p=0.002). Two of 13 patients died because of IAP.

CONCLUSION

AML phenotype, thrombocytopenia, bloodstream infection, CRP value >9 mg/dL and pneumonia were associated with IBI according to our study. We found mortality rate in our patients as 4% similar as in the literature and in our cases, early clinical and laboratory factors significantly associated with death were presence of AML (p=0.01) and invasive bacterial infection (p=0.038).

The study has several limitation. The study was a retrospective trial and the duration of neutropenia could not be determined which is also an important factor for IBI.

The authors have no conflicts of interest relevant to this article.

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