RESEARCH ARTICLE

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# Etiology and Factors Affecting Severe Complications and Mortality of Febrile Neutropenia in Children with Acute Leukemia

## Akut Lösemili Çocuklarda Febril Nötropeni Etiyolojisi ile Ciddi Komplikasyon ve Mortalite Üzerine Etkili Faktörler

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## Abstract

**Objective:** Febrile neutropenia (FN) is an important complication that causes high rates of morbidity and mortality in patients with malignancies. We aimed to investigate the etiology, epidemiological distribution and its change over the years, clinical courses, and outcomes of FN in children with acute leukemia.

**Materials and Methods:** We retrospectively analyzed the demographic data, clinical characteristics, laboratory results, severe complications, and mortality rates of pediatric patients with FN between January 2010 and December 2020.

**Results:** In 153 patients, a total of 450 FN episodes (FNEs) occurred. Eighty-four (54.9%) of these patients were male, the median age of the patients was 6.5 (range: 3-12.2) years, and 127 patients (83%) were diagnosed with acute lymphoblastic leukemia. Fever with a focus was found in approximately half of the patients, and an etiology was identified for 38.7% of the patients. The most common fever focus was bloodstream infection (n=74, 16.5%). Etiologically, a bacterial infection was identified in 22.7% (n=102), a viral infection in 13.3% (n=60), and a fungal infection in 5.8% (n=26) of the episodes. Twenty-six (23.2%) of a total of 112 bacteria were multidrug resistant (MDR) The rate of severe complications was 7.8% (n=35) and the mortality rate was 2% (n=9). In logistic regression analysis, refractory/relapsed malignancies and high C-reactive protein (CRP) at first admission were found to be the most important independent risk factors for mortality. Prolonged neutropenia after chemotherapy, diagnosis of acute myeloid leukemia, identification of fever focus or etiological agents, invasive fungal infections, polymicrobial infections, and need for intravenous immunoglobulin treatment increased the frequency of severe complications.

**Conclusion:** We found that there was no significant change in the epidemiological distribution or frequency of resistant bacteria in

## Öz

**Amaç:** Febril nötropeni (FN), malignitesi olan hastalarda morbidite ve mortaliteye neden olan en önemli komplikasyonlardan biridir. Akut lösemili çocuklarda FN etiyolojisini, epidemiyolojik dağılımını ve yıllar içindeki değişimini, klinik seyrini ve sonuçlarını araştırmayı amaçladık.

**Gereç ve Yöntemler:** Ocak 2010 ile Aralık 2020 arasında FN'li çocuk hastaların demografik verilerini, klinik özelliklerini, laboratuvar sonuçlarını, ciddi komplikasyonlarını ve ölüm oranlarını retrospektif olarak inceledik.

**Bulgular:** Yüz elli üç hastada toplam 450 FN epizodu (FNE) meydana geldi. Bu hastaların 84'ü (%54,9) erkekti, hastaların ortanca yaşı 6,5 (3-12,2) yıldı ve 127 hastaya (%83) akut lenfoblastik lösemi tanısı kondu. Ateş odağı hastaların yaklaşık yarısında vardı ve hastaların %38,7'sinde etiyolojik bir mikroorganizma saptandı. En sık görülen ateş odağı kan dolaşımı enfeksiyonuydu (n=74, %16,5). Etiyolojik olarak epizotların %22,7'sinde (n=102) bakteriyel enfeksiyon, %13,3'ünde (n=60) viral enfeksiyon ve %5,8'inde (n=26) mantar enfeksiyonları saptandı. Toplam 112 bakterinin 26'sı (%23,2) antibiyotiğe dirençliydi. Ciddi komplikasyon oranı %7,8 (n=35) ve mortalite oranı %2 (n=9) idi. Lojistik regresyon analizinde refrakter/relaps maligniteler ve ilk başvuruda yüksek C-reaktif protein (CRP) mortalite için en önemli bağımsız risk faktörleri olarak bulundu. Kemoterapi sonrası uzamış nötropeni, akut myeloid lösemi tanısı, ateş odağı veya etiyolojik ajanların saptanması, invaziv mantar enfeksiyonları, polimikrobiyal enfeksiyonlar ve intravenöz immünoglobulin tedavisi ciddi komplikasyon sıklığını artırdı.

**Sonuç:** Son 10 yılda merkezimizde dirençli bakterilerin epidemiyolojik dağılımında veya sıklığında önceki yıllara göre anlamlı bir değişiklik olmadığını saptadık. Uzamış ateş süresi, refrakter/relaps maligniteler,

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our center in the last 10 years compared to previous years. Prolonged duration of fever, relapsed/refractory malignancies, presence of fever focus, and high CRP level were significant risk factors for poor clinical course and outcome.

**Keywords:** Febrile neutropenia, Risk factors, Mortality, Infectious diseases, Pediatric cancer

ateş odağının varlığı ve yüksek CRP düzeyi kötü klinik seyir ve sonuçlar için önemli risk faktörleriydi.

**Anahtar Sözcükler:** Febril nötropeni, Risk faktörleri, Mortalite, Enfeksiyon hastalıkları, Çocukluk çağı kanseri

## Introduction

Febrile neutropenia (FN) is the most common complication that causes high morbidity and mortality in pediatric patients with malignancies [1]. However, a remarkable decrease in mortality has recently been observed due to the administration of broad-spectrum antibiotics and various approaches in supportive care [2]. For most pediatric patients with FN, the underlying focus of infection cannot be clinically or microbiologically documented [3,4]. Although fever can be a sign of serious infection during neutropenia, most individuals do not have a significant infection or sepsis [5,6]. Epidemiological data and agents causing infections in cases of FN can change across regions and over time, affecting the management and outcomes of these patients. Therefore, each center needs to closely monitor its data to plan management strategies against FN.

In addition, risk groups are more clearly defined for adults with FN, while there is still a lack of knowledge on this subject in children. Furthermore, biomarkers for use in pediatric cases are not yet clearly defined [4]. For a better understanding of these issues, more data are needed about the etiologies, clinical courses, and outcomes of FN in children [5]. For patients with a low risk for severe infections, outpatient management or early discontinuation of antibiotics in the hospital is increasingly reported in the literature [4].

In this study, we aimed to investigate the etiology, epidemiological distribution and its change over the years, clinical courses, and outcomes of FN in children with acute leukemia.

## Materials and Methods

This retrospective cohort study was conducted at Dokuz Eylül University Children's Hospital in İzmir, Türkiye. We included patients with acute leukemia under the age of 18 years who were diagnosed with FN between January 2010 and December 2020. Patients were treated with acute lymphoblastic leukemia (ALL)-BFM or acute myeloid leukemia (AML)-BFM protocols. Demographic data, clinical characteristics, laboratory results, antibiotic treatments, severe complications, and mortality data were collected from the medical records of the patients. FN episodes (FNEs) that occurred after hematopoietic stem cell transplantation were excluded from the study.

FN was defined as a single oral temperature of ≥38.3 °C or a temperature of ≥38.0 °C sustained over 1 hour in patients who had an absolute neutrophil count (ANC) of <500/mm$^3$ or ANCs between 500 and 1000/mm$^3$ expected to decrease below 500/mm$^3$ within 48 hours [7]. FNEs were determined as the time from the diagnosis of FN to the completion of antibiotic therapy, resumption of chemotherapy, or discharge of the patient, whichever was earliest. According to this definition, more than one FNE could be diagnosed during the same period of neutropenia [8]. After the physical examination at the time of first admission, the complete blood count, acute phase reactants, liver and renal function tests, urinalysis results, and blood and urine cultures were studied for all patients. In patients with central venous catheters (CVCs), paired blood samples, drawn from the catheter and a peripheral vein, were cultured before the initiation of antimicrobial therapy.

Fever without a known source was defined as an undetected fever focus even after physical examination, laboratory evaluation, and the application of imaging methods. Lower respiratory tract infection (LRTI) was defined as the presence of symptoms and signs of LRTI on physical examination or by imaging methods [9]. Upper respiratory tract infection (URTI) was defined by respiratory viral multiplex polymerase chain reaction (PCR) test positivity in patients who had respiratory symptoms [9]. Bacterial and fungal agents were microbiologically identified from a sterile site (blood, urine, stool, or bronchoalveolar lavage samples) or tissue cultures. Bacterial species identification was performed with an automatic culture system (VITEK). Bacterial growth (one or more) in blood cultures was defined as bloodstream infection (BSI). Members of the normal skin flora, such as coagulase-negative staphylococci, were considered causative based on their growth in at least two cultures. Catheter-associated BSI (CLABSI) was described in line with the recommendations of the Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection [10]. Urinary tract infection (UTI) was defined by urine culture positivity. Multidrug resistant (MDR) bacteria were defined by susceptibility test results using test methods and procedures according to the standards of the Clinical Laboratory Standards Institute (CLSI) [11].

Among the viral agents, herpes simplex virus 1-2 (HSV 1-2) and cytomegalovirus were detected based on PCR positivity.

Respiratory viruses [rhinovirus, respiratory syncytial virus (RSV), influenza, parainfluenza, human metapneumovirus, seasonal coronavirus, enterovirus, parechovirus, adenovirus, bocavirus, and SARS-CoV-2] were investigated by reverse transcription PCR tests performed with nasopharyngeal swab samples.

Neutropenic patients whose fevers were still maintained at the 96$^{th}$ hour of broad-spectrum antibiotic therapy were evaluated for fungal infections. Invasive fungal diseases (IFDs) were classified as possible, probable, and proven in line with the recommendations of the 8$^{th}$ European Conference on Leukemia Infections [12]. Empirical antifungal therapy was added for neutropenic patients with fever without a known source who did not respond to broad-spectrum antibacterial agents. Empirical antifungal therapy was discontinued if there was no evidence of IFD or no fever response [12]. Polymicrobial infections were diagnosed based on the identification of more than one pathogen by microbiological methods. Antimicrobial prophylaxis was administered to selected patients according to the recommendations of the 2010 guidelines of the Infectious Diseases Society of America [7]. Empirical antibiotic treatments were decided according to the clinical findings and previous bacterial growths of the patients. Granulocyte-colony stimulating factor (G-CSF) treatment was applied according to antineoplastic protocol recommendations [13].

Severe complications were considered as conditions such as oxygen requirements, hypotension, shock, inotrope requirements, intensive care unit admission, and mechanical ventilation requirements during FNEs [14]. Deaths occurring during FNEs were considered as mortality. The total duration of neutropenia was defined as the time from neutropenia that started after chemotherapy to the time that the neutrophil count reached 500 cells/mm$^3$. The post-fever neutropenia duration was determined as the time from the onset of fever in neutropenic patients to the time that the neutrophil count reached 500 cells/mm$^3$.

### Ethics

This study was approved by the local ethics committee and performed according to the principles of the Declaration of Helsinki. Informed written consent was not obtained because of the retrospective nature of the study.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 28 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to investigate whether the continuous variables were normally distributed. Descriptive statistics were presented using means ± standard deviations or medians (minimum-maximum values) regarding the distribution of variables. If variables were normally distributed, an independent samples t-test was used, and if they were not normally distributed, the Mann-Whitney U test was used to compare two independent groups. Chi-square or Fisher exact tests were used for comparisons between categorical variables. The variables found to be significant for bacteremia after univariate analysis (leukocyte count, presence of a central line, severity of neutropenia at admission, presence of previous FNE(s), positivity in peripheral blood, and CVC/implantable port cultures during the previous 3 months) were included in regression analyses (enter model) to explore independent risk factors for bacteremia. The receiver operating characteristics (ROC) curve was used to assess the prediction accuracy. The area under the curve (AUC), specificity, and sensitivity were also determined. Values of $p<0.05$ were considered statistically significant.

## Results

Among 176 patients diagnosed with acute leukemia, 23 (13%) had no FNEs. A total of 450 FNEs occurred in 153 patients, 84 (54.9%) of whom were male. The median age of these patients at the time of the first FNE was 6.5 (range: 3-12.2) years; 127 patients (83%) had ALL and 26 (17%) had AML. The number of FNEs was a median of two (1-11) per patient, and 51.3% (n=194) of the FNEs occurred in cases of high-risk ALL. Fifty-nine (13.1%) patients had relapsed/refractory leukemia. In 236 (52.4%) of all FNEs, the patients were in the induction phase of chemotherapy. The diagnosis of FN was made a median of 4 (1-8) days after chemotherapy. In 211 (46.9%) of all FNEs, patients had applied to outpatient clinics, and the remaining cases were diagnosed during hospitalization. The median total duration of the febrile period during FNEs was 2 (1-5) days. The median total neutropenic period after chemotherapy was 14 (7-26) days and the duration of neutropenia after the fever was 7.5 (5-13) days (Table 1).

There was no focus of fever in 234 (52%) FNEs. The most common focuses of fever were BSIs (n=74, 16.5%), URTIs (n=43, 9.6%), LRTIs (n=34, 7.6%), and UTIs (n=25, 5.6%), respectively. Twenty-one (28.4%) of the BSIs were catheter-related. More than one focus of fever was observed in 24 (5.3%) FNEs (Table 2). Etiologically, bacterial infections were identified in 22.7% (n=102), viral infections in 13.3% (n=60), and fungal infections in 5.8% (n=26) of the episodes. More than one pathogen was detected in 18 (4%) FNEs. Of the 112 bacteria identified, 72 (64.3%) were gram-negative pathogens, and 23.2% (n=26) of total bacteria and 33.3% (n=24) of gram-negative bacteria had antibiotic resistance patterns (Table 3). The rate of MDR bacteria was 14.8% (n=8) between 2010 and 2015, and it increased to 24% (n=18) between 2016 and 2020, but this difference was not statistically significant ($p>0.05$). Four (15.3%) of the 26 IFDs were proven (2 cases of aspergillosis, 1 mucormycosis, 1 *Candida* spp.), while the rest were possible or probable IFDs (Table 3). We could not identify an etiological cause in 236 (61.3%) of FNEs. The distributions of bacterial, fungal, and viral pathogens by years are shown in Figure 1.

**Table 1. Demographic, clinical, and laboratory characteristics and empirical antibiotic treatments administered for patients with febrile neutropenia episodes.**

| Baseline characteristics | n (%) |
|---|---|
| Median age, years (range) | 6.5 (3-12.2) |
| Male/female | 84/69 |
| **Types of leukemia** | |
| ALL | 127 (83%) |
| AML | 26 (17%) |
| **Phase of the last chemotherapy in FNEs** | |
| Induction | 236 (52.4%) |
| Consolidation | 172 (38.2%) |
| Maintenance | 20 (4.4%) |
| Reinduction | 22 (4.9%) |
| Relapsed/refractory malignancy | 59 (13.1%) |
| **Admission** | |
| Outpatient | 211 (46.9%) |
| During hospitalization | 239 (53.1%) |
| **Central venous catheter** | 251 (55.8%) |
| Hickman catheter | 24 (5.4%) |
| Port catheter | 227 (50.4%) |
| Mucositis | 156 (34.7%) |
| Duration since last chemotherapy (days) | 4 (1-8) |
| Total duration of fever (days) | 2 (1-5) |
| Total neutropenia length after chemotherapy (days) | 14 (7-26) |
| Duration of neutropenia after fever (days) | 7.5 (5-13) |
| G-CSF | 259 (57.7%) |
| **Laboratory results** | |
| TLC/mm$^3$ (median, 25$^{th}$-75$^{th}$ percentiles) | 700 (400-1100) |
| ANC/mm$^3$ (median, 25$^{th}$-75$^{th}$ percentiles) | 100 (0-200) |
| ALC/mm$^3$ (median, 25$^{th}$-75$^{th}$ percentiles) | 400 (200-800) |
| AMC/mm$^3$ (median, 25$^{th}$-75$^{th}$ percentiles) | 0 (0-100) |
| Platelets/mm$^3$ (median, 25$^{th}$-75$^{th}$ percentiles) | 51000 (24000-88250) |
| Hemoglobin, g/dL (median, 25$^{th}$-75$^{th}$ percentiles) | 8.9 (8-10.3) |
| CRP, mg/L (median, 25$^{th}$-75$^{th}$ percentiles) | 26.1 (10-73.1) |
| **Empirical antibiotic treatments** | |
| **Single agent** | 182 (40.4%) |
| Meropenem | 73 (16.2%) |
| Piperacillin/tazobactam | 109 (24.2%) |
| **Two agents** | 212 (47.1%) |
| Meropenem with aminoglycoside | 149 (33.1%) |
| Piperacillin/tazobactam with aminoglycoside | 15 (3.3%) |
| Meropenem with glycopeptide | 35 (7.8%) |
| Piperacillin/tazobactam with glycopeptide | 13 (2.9%) |
| **Three agents** | 56 (12.5%) |
| Meropenem and aminoglycoside with glycopeptide | 56 (12.5%) |

ALL: Acute lymphoblastic leukemia, AML: acute myeloid leukemia, FNE: febrile neutropenia episode, TLC: total leukocyte count, ALC: absolute lymphocyte count, AMC: absolute monocyte count, ANC: absolute neutrophil count, CRP: C-reactive protein, G-CSF: granulocyte colony-stimulating factor.

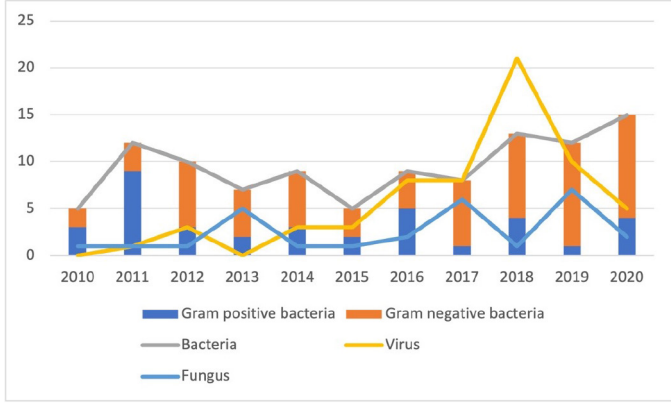


**Figure 1.** Distributions of bacterial, fungal, and viral pathogens in febrile neutropenia episodes by years.

**Table 2. Distribution of fever focus in febrile neutropenia episodes of pediatric patients with acute leukemia.**

| Focus of the fever | n (%) |
|---|---|
| None | 234 (52%) |
| **Bloodstream infection** | 74 (16.5%) |
| Catheter-unrelated | 53 (11.8%) |
| Catheter-related | 21 (4.7%) |
| URTI | 43 (9.6%) |
| LRTI | 34 (7.6%) |
| UTI | 25 (5.6%) |
| Acute gastroenteritis | 21 (4.7%) |
| **Invasive fungal infection** | 26 (5.8%) |
| Candidemia | 1 (0.2%) |
| Invasive pulmonary aspergillosis | 24 (5.3%) |
| Sinopulmonary mucormycosis | 1 (0.2%) |
| Typhlitis | 5 (1.1%) |
| Pancreatitis | 3 (0.7%) |
| CMV viremia | 6 (1.3%) |
| Chickenpox | 1 (0.2%) |
| Infective endocarditis | 1 (0.2%) |
| Mastoiditis | 1 (0.2%) |
| Presence of more than one focus of fever | 24 (5.3%) |

URTI: Upper respiratory tract infection, LRTI: lower respiratory tract infection, UTI: urinary tract infection, CMV: cytomegalovirus.

G-CSF was administered in 259 of the FNEs (57.7%). The durations of total neutropenia, post-fever neutropenia, and fever were shorter in patients who received G-CSF compared to those who did not (p<0.001, p<0.001, and p<0.001, respectively).

A negative correlation was found between the duration of fever and both total leukocyte count (TLC) and absolute monocyte count in the first complete blood count performed at the time of admission (p=0.048 and p<0.001, respectively). A positive correlation was found between the duration of fever and duration of neutropenia (p<0.001). While the duration of total

**Table 3. Isolated pathogens and Multidrug resistant bacteria identified in febrile neutropenia episodes of pediatric patients with acute leukemia.**

| **Bacterial pathogens (n=112, 22.7%)*** | | **n (%)** |
|---|---|---|
| **Gram-positive bacteria (n=39, 34.8%)** | Coagulase-negative staphylococci | 29 (25.9%) |
| | Methicillin-sensitive *Staphylococcus aureus* | 4 (3.5%) |
| | *Enterococcus* spp. | 6 (5.3%) |
| | *Enterococcus faecium* | 3 (2.6%) |
| **Gram-negative bacteria (n=72, 64.3%)** | E*scherichia coli* | 41 (36.6%) |
| | *Pseudomonas aeruginosa* | 7 (6.2%) |
| | *Klebsiella pneumoniae* | 7 (6.2%) |
| | *Klebsiella oxytoca* | 4 (3.5%) |
| | *Stenotrophomonas maltophilia* | 3 (2.6%) |
| | *Pseudomonas stutzeri* | 2 (1.8%) |
| | *Acinetobacter lwoffii* | 2 (1.8%) |
| | *Salmonella* spp. | 2 (1.8%) |
| | *Ralstonia pickettii* | 2 (1.8%) |
| | *Proteus mirabilis* | 1 (0.9%) |
| **Others (n=1, 0.9%)** | *Mycoplasma pneumoniae* | 1 (0.9%) |
| **Multidrug resistant bacteria** | **n (%)** | |
| **Gram-negative bacteria** | | |
| ESBL-producing *Escherichia coli* | 12 (10.7%) | |
| ESBL-producing *Klebsiella* spp. | 4 (3.6%) | |
| IBL-producing *Pseudomonas aeruginosa* | 4 (3.6%) | |
| Carbapenem-resistant *Klebsiella* spp. | 2 (1.8%) | |
| Carbapenem-resistant *Escherichia coli* | 1 (0.9%) | |
| MDR *Pseudomonas aeruginosa* | 1 (0.9%) | |
| **Gram-positive bacteria** | | |
| Vancomycin-resistant enterococci | 2 (1.8%) | |
| **Total** | 26 (23.2%) | |
| **Viral pathogens (n= 60, 13.3%)** | | **n (%)** |
| **Viral respiratory infection agents** | Rhinovirus | 26 (43.3%) |
| | RSV | 9 (15%) |
| | Influenza | 8 (13.3%) |
| | Bocavirus | 4 (6.6%) |
| | Coronavirus | 3 (5%) |
| | Metapneumovirus | 2 (3.3%) |
| | SARS-CoV-2 | 1 (1.6%) |
| **CMV** | | 7 (11.7%) |
| **Herpes simplex virus** | | 2 (3.3%) |
| **Fungal infections (n=26, 5.8%)** | | **n (%)** |
| **Invasive pulmonary aspergillosis** | Possible | 2 (7.7%) |
| | Probable | 20 (77%) |
| | Proven | 2 (7.7%) |
| **Candidemia** | | 1 (3.8%) |
| **Sinopulmonary mucormycosis** | | 1 (3.8%) |
| **Presence of more than one pathogen in etiology**** | | **18 (4%)** |

ESBL: Extended-spectrum β-lactamase, IBL: inducible β-lactamase, MDR: multidrug-resistant, RSV: respiratory syncytial virus, CMV: cytomegalovirus, PCR: polymerase chain reaction.

*: More than one bacterium was identified in 7 febrile neutropenia episodes.

**: The most common combinations of etiological agents were bacterial-viral (n=6), viral-fungal (n=4), and bacterial-fungal (n=4). We identified bacterial-viral-fungal infections in two febrile neutropenia episodes.

fever was longer in patients with mucositis (p=0.004), there was no relationship between mucositis and bacteremia, gram-positive infections, or IFDs (p=0.847, p=0.676, and p=0.676, respectively).

Trimethoprim-sulfamethoxazole prophylaxis was given in 377 (83.8%) of 450 FNEs. When FN was diagnosed, patients were using ciprofloxacin in 6% and cefixime in 0.7% of the episodes as antibiotic prophylaxis. When patients who received and did not receive antibiotic prophylaxis were compared, the incidence of bacterial infection was similar (22.8% vs. 22%, p>0.05). Monotherapy was used in the empirical treatment of 182 (40.4%) FNEs (Table 1). Antibiotic coverage remained first-line antibiotics in 173 (38.4%) of 450 episodes and an increase was required in 261 (58%). The CVC was removed in 8 (1.8%) of 21 CLABSIs (n=5 with coagulase-negative staphylococci, n=1 with methicillin-sensitive *Staphylococcus aureus*, n=1 with *Stenotrophomonas maltophilia*, n=1 with *Ralstonia pickettii*) and antibiotic lock therapy was administered in 13 (2.9%) FNEs (n=10 with vancomycin, n=3 with ciprofloxacin).

Antifungal prophylaxis was used in 407 (90.4%) of 450 FNEs. The most frequently used agents were fluconazole (63.8%), liposomal amphotericin B (11.8%), and voriconazole (9.1%), respectively. We observed that patients who received fluconazole and liposomal amphotericin B prophylaxis were diagnosed with fewer IFDs than those who did not receive such prophylaxis (p=0.019 and p=0.023, respectively). Empirical antifungal therapy was added in 144 (32%) of the FNEs. The most frequently used agents for treatment were echinocandins (n=51, 11.4%), liposomal amphotericin B (n=47, 10.5%), and azole groups (9.4%, n=42; voriconazole, n=22; fluconazole, n=20), respectively. Empirical antifungal treatments were revised in 42 (29.1%) of the FNEs due to allergic reactions, adverse events, or evidence of mold or yeast species. Antiviral therapy (acyclovir, ganciclovir, or oseltamivir) was used in 19.6% (n=88) of the FNEs.

The median treatment duration for FNEs was 10 (7-17) days. Intravenous immunoglobulin (IVIG) was given in 43 (9.6%) episodes, and granulocyte suspensions were given in 11 (2.4%) episodes as a supportive treatment. We found the incidence of severe complications to be 7.8% (n=35) and the mortality rate to be 2% (n=9) among all FNEs. Demographic data, clinical features, and laboratory results of patients in terms of mortality and severe complications are compared separately in Table 4. The rate of severe complications was higher in patients with AML than those with ALL (16.7% vs. 6.1%, p=0.002). However, mortality rates were similar between the two groups (4.2% vs. 1.6%, p=0.161).

In logistic regression analysis, prolonged fever, relapsed/refractory malignancies, presence of fever focus, and need for IVIG treatment were found as independent risk factors for the development of complications among the associated significant covariates described above. In addition, relapsed/refractory malignancies, need for IVIG treatment, and high C-reactive protein (CRP) levels at the time of first admission were found as independent risk factors for mortality in FNEs among the significant covariates (Table 5). The AUC of CRP for predicting mortality was 0.754 (95% confidence interval: 0.593-0.916, p=0.009) in the ROC curve (Figure 2). The sensitivity of predicting mortality with a CRP cut-off value of 93.6 mg/L was 66.7% and the specificity was 81.9%.

## Discussion

In this study, which included a large cohort of children with acute leukemia, about half of the FNEs had no focus of fever and an etiological cause was microbiologically detected in 38.7% of the episodes. Among them, bacterial infections were identified in 22.7%, viral infections in 13.3%, and fungal infections in 5.8% of the episodes. We observed severe complications and mortality at rates of 7.8% and 2%, respectively. The mortality rate was higher among patients with longer durations of fever and post-fever neutropenia, and among those with high-risk or relapsed/resistant malignancies. While prolonged neutropenia after chemotherapy, AML diagnosis, identification of fever focus or etiological agents, invasive fungal infections, polymicrobial infections, and G-CSF treatment increased the frequency of severe complications, they did not increase mortality. We found that severe complications and mortality were increased among patients with prolonged total durations of fever and post-fever neutropenia, lower TLC at first admission, relapsed/refractory malignancies, FN occurring during hospitalization, and need for IVIG. The mortality rate was higher among patients with lower TLC and absolute lymphocyte count and higher CRP values at the time of first admission.

In the literature, a fever focus could not be shown in 53%-79% of FNEs, and infections are microbiologically confirmed in only 15%-38% of cases [15,16,17,18,19]. It was previously reported that patients without fever focus had milder clinical courses and were at lower risk in terms of morbidity and mortality [17,20,21,22]. Similar results were demonstrated in our study. Before defining the focus of fever as absent, a careful investigation should be performed. We observed that the frequency of severe complications was higher among patients with a fever focus; such patients should be monitored more closely.

The focus of fever in FNEs in patients with hematological malignancies is commonly BSI, and its frequency was previously reported as 11%-38% [18,23]. Although there has been a shift from gram-negative bacteria to gram-positive bacteria over the last few decades, each center has its own unique epidemiological features that may change over time [24]. In a previous study

**Table 4. Univariate analysis of risk factors of severe complications and mortality in children with febrile neutropenia.**

| | Severe complications | | | Mortality | | |
|---|---|---|---|---|---|---|
| | Yes (n=35) | No (n=415) | p | Yes (n=9) | No (n=441) | p |
| Total duration of the fever (days) (median, 25th-75th percentiles) | 5 (0-6) | 2 (1-4) | **p<0.001** | 4 (3-10) | 2 (1-5) | **p=0.014** |
| Total duration of neutropenia after chemotherapy (days) | 23 (13-35) | 14 (7-26) | **p=0.002** | 23 (19-38) | 14 (7-26) | p>0.05 |
| Post-fever neutropenia duration (days) | 12 (6-24) | 7 (5-13) | **p=0.008** | 12 (7.5-30.5) | 7 (5-13) | **p=0.019** |
| Days since last chemotherapy, median | 2 (0-6) | 4 (1-7) | p>0.05 | 1 (0-13.5) | 4 (1-7) | p>0.05 |
| TLC/mm$^3$ (median, 25th-75th percentiles) | 500 (200-800) | 700 (400-1100) | **p=0.042** | 200 (100-700) | 700 (400-1100) | **p=0.007** |
| ANC/mm$^3$ (median, 25th-75th percentiles)*,** | 0 (0-100) | 100 (0-200) | p>0.05 | 0 (0-100) | 100 (0-200) | p>0.05 |
| ALC/mm$^3$ (median, 25th-75th percentiles) | 400 (100-600) | 400 (200-800) | p>0.05 | 0 (0-600) | 400 (200-800) | **p=0.021** |
| AMC/mm$^3$ (median, 25th-75th percentiles) | 0 (0-0) | 0 (0-100) | p>0.05 | 0 (0-0) | 0 (0-100) | p>0.05 |
| Platelets/mm$^3$ (median, 25th-75th percentiles)*,** | 34000 (20000-82000) | 52000 (26500-90500) | p>0.05 | 28000 (14500-58500) | 51000 (25000-90000) | p>0.05 |
| CRP, mg/dL (median, 25th-75th percentiles) | 47 (9.6-115.7) | 26 (10.4-68.3) | p>0.05 | 100.9 (36.8-204.9) | 26 (10-68.8) | **p=0.009** |
| High-risk malignancy | 54.3% (19) | 53% (220) | p>0.05 | 88.9% (8) | 52.4% (231) | **p=0.04** |
| Induction period of malignancy | 71.4% (25) | 50.8% (211) | **p=0.019** | 33.3% (3) | 47.8% (211) | p>0.05 |
| Relapsed/refractory malignancies | 40% (14) | 10.8% (45) | **p<0.001** | 77.8% (7) | 11.6% (52) | **p<0.001** |
| Diagnosed with FN during hospitalization | 77.1% (27) | 51.1% (212) | **p=0.003** | 88.9% (8) | 52.4% (231) | **p=0.04** |
| Focus of fever | 82.9% (29) | 45.1% (187) | **p<0.001** | 66.7% (6) | 47.6% (210) | p=0.323 |
| Identified etiological agents | 57.1% (20) | 37.1% (154) | **p=0.019** | 33.3% (3) | 38.8% (171) | p=1 |
| Invasive fungal infections | 17.1% (6) | 4.8 (20) | **p=0.011** | 0% (0) | 5.9% (26) | p=1 |
| Bacterial infection | 28.6% (10) | 22.2% (92) | p=0.385 | 11.1% (1) | 22.9% (101) | p=0.691 |
| Resistant bacterial infections | 5.7% (2) | 8% (33) | p=1 | 11.1% (1) | 7.7% (34) | p=0.521 |
| Viral infections | 22.9% (8) | 12.5% (52) | p=0.114 | 22.2% (2) | 13.2% (58) | p=0.342 |
| Polymicrobial infections | 17.1% (6) | 4.8% (20) | **p=0.011** | 0% (0) | 5.9% (26) | p=1 |
| IVIG requirement | 37.7% (13) | 7.2% (30) | **p<0.001** | 44.4% (4) | 8.8% (39) | **p=0.006** |
| G-CSF | 77.1% (27) | 56% (237) | **p=0.015** | 77.8% (7) | 57.3% (252) | p=0.313 |

ALL: Acute lymphoblastic leukemia, TLC: total leukocyte count, ANC: absolute neutrophil count, ALC: absolute lymphocyte count, AMC: absolute monocyte count, CRP: C-reactive protein, FN: febrile neutropenia, IVIG: intravenous immunoglobulin, G-CSF: granulocyte colony-stimulating factor.

*: When the neutrophil count was grouped below 100 and between 100 and 500 (p=0.116) and when the platelet count was grouped below 50000 and above (p=0.208), no relationship was found with the frequency of complications.

**: When the neutrophil count was grouped below 100 and between 100 and 500 (p=0.222) and when the platelet count was grouped below 50000 and above (p=0.09), no effect on mortality was observed.

**Table 5. Multiple logistic regression analysis of risk factors associated with complications and mortality in febrile neutropenia episodes.**

| Independent risk factors for complications | Odds ratio | Confidence interval (95%) | p |
|---|---|---|---|
| IVIG requirement | 3.287 | 1.295-8.345 | **0.012** |
| Total duration of fever | 1.136 | 1.038-1.243 | **0.006** |
| Relapsed malignancy | 2.543 | 0.837-7.726 | 0.1 |
| Refractory malignancy | 11.427 | 3.617-36.103 | **<0.001** |
| Presence of focus of fever | 4.621 | 1.655-12.901 | **0.003** |
| **Independent risk factors for mortality** | **Odds ratio** | **Confidence interval (95%)** | **p** |
| IVIG requirement | 7.830 | 1.459-42.027 | **0.016** |
| CRP | 1.009 | 1.001-1.017 | **0.037** |
| Reslapsed malignancy | 3.244 | 0.264-39.919 | 0.358 |
| Refractory malignancy | 43.801 | 7.307-262.573 | **<0.001** |

IVIG: Intravenous immunoglobulin, CRP: C-reactive protein.

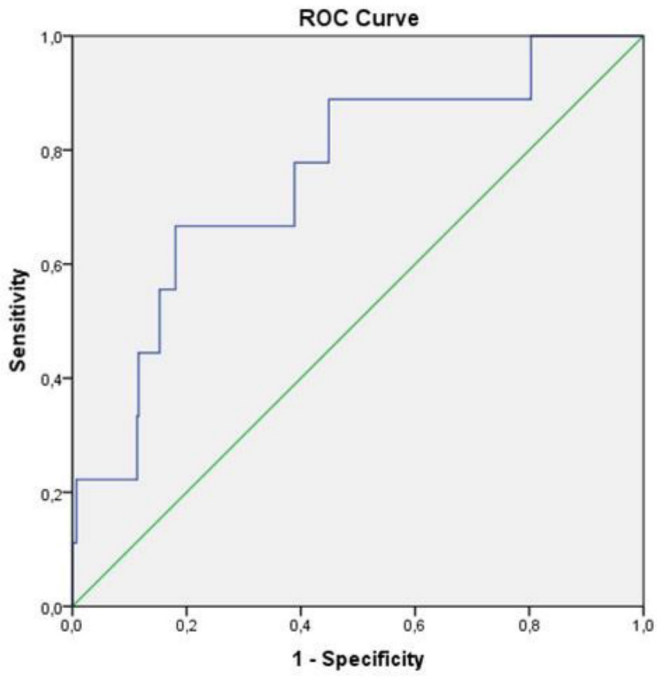


**Figure 2.** Receiver operating characteristics (ROC) curve for C-reactive protein in predicting mortality.

from our center, gram-negative bacteria were detected as the most frequent agents between 1995 and 2005. The most common gram-negative bacterial pathogens were *Escherichia coli* and *Klebsiella pneumoniae*, respectively [25]. Herein, we demonstrated that gram-negative bacteria were still dominant in our center and BSI was the most common focus of fever among bacterial pathogens. The frequency of *Escherichia coli* (from 23.9% to 36.6%) and *Pseudomonas aeruginosa* (5.6% to 6.2%) increased, and the frequency of *Klebsiella pneumoniae* (from 16.9% to 6.2%) decreased in our center. Increased rates of MDR are being reported among gram-negative bacteria that cause infections in FNEs [26,27]. In particular, concerns have been raised regarding multidrug-resistant (MDR) *Pseudomonas aeruginosa* infections, which have been on the rise since the 2000s [28]. Infections caused by antibiotic-resistant gram-negative bacteria were reported to be associated with longer hospitalization, poor prognosis, and increased mortality [27,29]. Although we showed an increment in the incidence of *Pseudomonas* and *Escherichia coli*, we did not find a statistically significant increase in MDR gram-negative bacteria when we analyzed our data for the last 10 years. In our study, there was no relationship between MDR bacterial infections and severe complications or mortality. This may be due to the early initiation of antimicrobial therapy with appropriate coverage. In addition, another reason may be that we see less frequent patterns of resistance to carbapenem or MDR cases, which are more difficult to treat.

In the literature, the frequency of viral etiology was reported in a wide range of 8% to 76% among cancer patients with neutropenia [15,17,30,31,32,33]. Rhinovirus and RSV, which are respiratory tract viruses, were shown to be the most frequent agents among the identified viruses [9,31,32]. Although some studies showed that respiratory viruses did not increase the rates of morbidity and mortality, their clinical significance in this at-risk patient group has not been fully determined [9,34]. This wide distribution of viral pathogens can be attributed to the diversity of study methods. The frequency of viral pathogens in the present study was similar to those found in previous reports using similar methods [17,31,33]. Additionally, we found that viral pathogens identified in the etiology of FNEs did not increase the risk of severe complications and mortality. Early discontinuation of antibiotic therapy may be considered after the detection of only the viral pathogen in patients with FN, but there is no definitive information on this subject in the literature [32]. In several studies, viral and bacterial infections were shown to coexist in FNEs [31,32]. In our study cohort, viral pathogens were accompanied by bacterial and/or fungal infections in 2.7% of FNEs. For this reason, it should be kept in mind that viral agents may be a part of polymicrobial infections. Hakim et al. [15] reported a frequency of polymicrobial infections of 10%. Koskenvuo et al. [31] showed that patients with both viral and bacterial pathogens in the same FNE had more severe clinical outcomes and required longer durations of antibiotic therapy. In our study, we found polymicrobial infections in 4% of FNEs and these infections increased the frequency of severe complications, but not the mortality rate. Therefore, these patients should be monitored more closely to diagnose and prevent complications.

In previous studies, the incidence of IFDs was reported between 2.1% and 11.2%, and mortality due to IFDs was up to 40% among pediatric patients with hematological malignancies [35,36,37,38]. The mortality rate among patients with both bacteria and fungi in the etiology was reported to be between 43% and 78% [35,39]. Guidelines strongly recommended administering systemic antifungal prophylaxis including mold-active drugs to reduce IFD-related morbidity and mortality in high-risk pediatric patients with malignancies [12]. The IFD frequency in our study was similar to that reported in the literature. Although IFDs increased the frequency of severe complications, they did not cause significant changes in the mortality rate. In this study, IFD did not cause mortality, but the presence of IFD was associated with severe problems despite the use of antifungal prophylaxis.

In recent years, various risk classifications have been used and short-term hospitalizations with close outpatient follow-up have been utilized for appropriate patients, particularly

in adults [40,41,42]. Although several methods to evaluate risk in pediatric patients with FN have been proposed in the literature, there is no strongly proven recommendation. A verification based on local conditions and epidemiological data is recommended before classification rules are used [33]. There is also a need for a better understanding of the epidemiology, etiology, clinical course, and outcome of children with FN to support the use of a specific risk classification. Hakim et al. [15] found a clinical complication rate of 14% in pediatric patients with FN. In recent studies of febrile neutropenic pediatric patients, the mortality rate has been reported between 0.5% and 6.6% [16,20,33,40,41,43,44,45]. In our study, we found a lower rate of severe complications (7.8%), and our mortality rate (2%) was close to the lower limit of the range reported in the literature. We showed that the most significant risk factors for severe complications were prolonged fever, relapsed/refractory malignancies, presence of fever focus, and treatment with IVIG in regression analyses. Mortality rates were higher in patients with refractory malignancies, high CRP values, and IVIG requirements. Therefore, these factors can be used in the risk evaluation and management of FNEs in pediatric patients.

The most significant strengths of our study were that it covered a wide period and included a large number of FNEs in children with only acute leukemia, which constituted a relatively homogeneous population. However, the retrospective nature of the study was its main limitation. Epidemiological studies are always needed to show the current data on FN. Therefore, prospective and larger studies including multicenter regional or country-based data are expected to further increase our knowledge on this subject.

## Conclusion

We found that there was no significant change in the epidemiological distribution or frequency of MDR bacteria in our center in the last 10 years compared to previous years. We also showed that the most common etiological cause was bacterial infection due to gram-negative pathogens and the most common focus of FN was BSI in our center in the last 10 years. Prolonged duration of fever, relapsed/refractory malignancies, presence of fever focus, and high CRP level were significant risk factors for poor clinical course and outcome. Evaluating the etiological and epidemiological data and outcomes of patients regularly is important in efforts to better manage FNE, improve quality of life, and reduce the complications and mortality rates of children with acute leukemia. For this purpose, each region should closely monitor its etiological distributions, epidemiological characteristics, and changes over time.

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### Ethics

**Ethics Committee Approval:** This study was approved by the local ethics committee (approval number: 2021/07-05) and performed according to the principles of the Declaration of Helsinki.

**Informed Consent:** Informed written consent was not obtained because of the retrospective nature of the study.

### Authorship Contributions

Surgical and Medical Practices- İ.C.E., A.Ç.G., Ş.Ö.A., H.K.A., Ş.A., C.Ö., N.B.; Concept- İ.C.E., Ş.Ö.A., H.K.A., Ş.A., C.Ö., Ö.T., Ş.Y.; Design- İ.C.E., A.Ç.G., H.K.A., İ.A., C.Ö., Ö.T., Ş.Y., H.Ö., N.B.; Data Collection or Processing- İ.C.E., A.Ç.G., Ş.Ö.A., İ.A., Ş.A.; Analysis or Interpretation- İ.C.E., İ.A., H.Ö., N.B.; Literature Search- İ.C.E., Ö.T., Ş.Y., H.Ö., N.B.

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