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Analyse of Febrile Neutropenia Attacks in Children with Acute Lymphoblastic Leukemia

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Abstract

Febrile neutropenia (FN) is the most important cause of morbidity and mortality during treatment in childhood with acute lymphoblastic leukemia (ALL). The aim of this retrospective study was to assess clinical features, outcomes, treatment modalities, documented infection rates, and frequency of isolation of specific organisms from ALL patients treated by our Department of Pediatric Hematology and Oncology using Berlin-Frankfurt-Munich (BFM) protocols. In this study 132 children diagnosed with ALL and treated according to the ALL-BFM 2009 protocol at Kayseri City Hospital, Department of Pediatric Hematology and Oncology between July 2015 and May 2022 were enrolled and evaluated for episodes of FN during intensive chemotherapy. Treatment characteristics, the presence of relapse, duration of neutropenia, culture results, the choice and duration of antibiotics, and disease prognosis were retrospectively assessed using patient records. In 132 acute leukemia cases, 278 episodes of FN were observed aged 1.1 and 17.8 years (mean 7.1±4.9 years) in a male to female ratio of 1.5:1. Infection focus could be documented in 66 episodes (23.7%); pulmonary infections in 23 patients (34.8%), gastrointestinal tract infections in 20 patients (30.3%), in 10 patients urinary tract infections (15.1%), derma¬otological and soft tissue infections in 2 patients (3%). The causative infectious agent could be demonstrated in 92 (33%) episodes. The most common site of isolation was blood (86/92, 30.9%). While the most frequently identified bacterial infectious agents were Gram-positive bacteria (56 isolates, 20.1%), Gram-negative bacteria were identified in 28 isolates (n=10%). Fungal growth was detected in 6 (2.1%) patients and polymicrobial growth was detected in 3 (1.1%) patients. Of the 132 patients, 4 (3%) died due to infection 2 died during induction, and 2 died during reinduction phases. Centers should evaluate their results to identify changing epidemiological patterns and to treat FN early and efficiently.

Keywords: Acute lymphoblastic leukemia, children, febrile neutropenia

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Introduction

Febrile neutropenia (FN), observed at the time of diagnosis and during therapy, is a major cause of death and delay in treatment in patients with acute lymphoblastic leukemia (ALL).[1] Cytotoxic chemotherapy and cancer itself, which alter humoral and cellular immunity, are the most common and important risk factors for FN, particularly when neutropenia is expected to last longer than seven days. Intensive chemotherapy also predisposes to infection by destroying important protective anatomical barriers such as the oral cavity and gastrointestinal mucosa and may facilitate translocation of enteric pathogens into the bloodstream. Corticosteroids, commonly used for therapy, also have adverse effects on the host immune system, predisposing to infections. Central venous lines (CVLs) are used almost routinely, resulting in a risk of catheter-related blood flow and local infections at the CVL site.[1,2]

The management of FN with early and efficient therapy and advances in supportive care have significantly improved survival and outcomes from infectious complications. Cancer type is considered in the risk assessment for major infections in the decision rules proposed in guidelines. In some studies in the literature, the results may differ due to the heterogeneity of the groups, solid tumor or hematological cancer. In particular, patients with ALL who receive induction therapy are considered high-risk patients.[2-4]

The aim of this retrospective study was to assess clinical features, outcomes, treatment modalities, documented infection rates, and frequency of isolation of specific organisms from ALL patients treated by our Department of Pediatric Hematology and Oncology using Berlin-Frankfurt-Munich (BFM) protocols. Experience sharing is needed to accurately and early predict the risk of complications and death in patients at higher risk of serious complications. The results of this study may guide the appropriate initiation and duration of therapies for febrile neutropenic attacks.

Material and Method

In this study 132 children diagnosed with ALL and treated according to the ALL-BFM 2009 protocol at Kayseri City Hospital, Clinic of Pediatric Hematology and Oncology between July 2015 and May 2022 were enrolled and evaluated for episodes of FN during intensive chemotherapy. Treatment characteristics, the presence of relapse, duration of neutropenia, blood culture results, the selection and duration of antibiotics, and disease prognosis were retrospectively assessed using patient records.

Neutropenia is defined as an absolute neutrophil count (ANC) <500/mm^3 or an ANC expected to decrease to <500/mm^3 within the next 48 hours. Fever is defined as a single temperature of 38.3 °C or two temperature recordings greater than or equal to 38 °C recorded at least 4 h apart. Even if the patient is afebrile on admission, fever at home is considered important.[3,5] Conditions such as severe abdominal pain, severe mucositis, rectal abscesses, shock, catheter tunnel infections, diarrhea, localized pain, impaired consciousness, and hemodynamic abnormalities that are considered a febrile neutropenic episode, especially receiving glucocorticoids, may result in a lower/intermittent rise in temperature. The physical examinations of the patients were comprehensive and repeated at least daily. Complete blood count, electrolytes, creatinine and blood urea nitrogen, liver transaminases, total bilirubin, albumin, blood and urine cultures, C-reactive protein, and procalcitonin determined for the patients. Blood cultures were taken from the catheter only, we did not receive additional peripheral blood cultures. If there is abdominal pain and diarrhea, we get a stool adenovirus, rotavirus antigen test, with some cases *Clostridioides difficile* antigen and stool culture. Abdominal ultrasonography is required for typhlitis. Anaerobic blood culture is not available at our institution. The patients received trimethoprim-sulfamethoxazole orally 3 days/week for *Pneumocystis jiroveci* pneumonia prophylaxis. Other than that, no routine prophylactic antibiotics or antifungal drugs were administered. Broad-spectrum empirical antibiotics (cefepime, meropenem, piperacillin-tazobactam) were administered promptly (always within 30 minutes after arriving at hospital). Aminoglycosides (amikacin) were added to initial therapy for signs of fever with chills indicative of Gram-negative sepsis, increased acute phase reactants, early Gram-negative signs from blood culture, and septic shock. Glycopeptides (teicoplanin, vancomycin) were added if fever persisted for 48-72 (but always 24-48 hours) hours after the start of the initial antibiotics, catheter-associated infections, methicillin-resistant *Staphylococcus aureus*/penicillin-resistant pneumococcal colonization, growth of Gram-positive bacteria in culture, hypotension, cardiovascular disorder, and presence of severe mucositis. We used empiric antifungal therapy (liposomal amphotericin B, caspofungin) in children who had recurrent or persistent fever for 72-96 hours after initiation of empiric broad-spectrum antimicrobial therapy, no identified source of fever, and ANC not increasing. Diagnosis of invasive fungal infection (IFI) was based on the European Organization for Research and Treatment of Cancer and Mycoses Study Group criteria.[3,5-9] There is no sequel to the first episode. With respiratory signs and symptoms, we cannot obtain a molecular analysis of seasonal respiratory viruses such as influenza and respiratory syncytial viruses. Acyclovir was started in patients with any suspicion of herpes simplex or zoster, or symptoms of esophagitis. Molecular analysis of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was performed during the pandemic.

Statistical Analysis

All statistical analyzes were performed using IBM SPSS Statistics 22.0 (IBM Corp.). Descriptive data were presented as means or medians calculated according to whether the distribution was normal or not. This retrospective study was approved by the Ethics Committee of Kayseri City Hospital (decision no: 643, date: 02.06.2022) and was performed in accordance with the ethical standards of the Declaration of Helsinki.

Results

In 132 acute leukemia cases, 278 episodes of FN were observed aged 1.1 and 17.8 years (mean 7.1±4.9 years) in a male to female ratio of 1.5:1. FN attacks were observed in 31.2% (n=87) of patients during induction therapy, in 33% (n=92) intensification/consolidation, 28% (n=78) reinduction, and in 7.5% (n=21) at relapse therapy. Four patients completed their treatment without FN. This corresponds to an overall rate of 2.2 episodes per patient. Median ANC in FN episodes was 237/mm^3 (0-496/mm^3). The median duration of neutropenia was 6.3 days (range 1-19 days). Patient demographics and clinical characteristics are summarized in **Table 1**.

Highlights

- Infections are the leading cause of morbidity and mortality during treatment for childhood acute lymphoblastic leukemia.
- With persistent neutropenia, patients are at particular risk for serious infectious complications and worse outcomes.
- Treatment of febrile neutropenia with early and efficient therapy and advances in supportive care have significantly improved survival and outcomes in infectious complications.

Infection focus could be documented in 66 episodes (23.7%); pulmonary infections in 23 patients (34.8%), gastrointestinal tract infections in 20 patients (30.3%), in 10 patients urinary tract infections (15.1%), skin and soft tissue infection in 2 patients (3%). Two patients had acute appendicitis and 1 patient had 2 acute pancreatitis attacks. A revision was required in 10 patients (7.6%) due to the catheter infection. Septic shock developed in 20 patients, 16 of them secondary to Gram-negative bacteremia.

The causative infectious agent could be demonstrated in 92 (33%) episodes. The most common site of isolation was blood (86/92, 30.9%). While the most frequently identified bacterial infectious agents were Gram-positive bacteria (56 isolates, 20.1%), Gram-negative bacteria were identified in 28 isolates (n=10%). Fungal growth was detected in 6 (2.1%) patients and polymicrobial growth was detected in 3 (1.1%) patients (**Table 2**). Growths that did not correlate with clinical findings were considered contagious.

Initial empiric antimicrobial therapy (cefepime, meropenem or piperacillin/tazobactam) with a combination of amikacin was used in 172 (61.8%) of the episodes, and the average duration of use of amikacin was 7.4 days. Glycopeptides (teicoplanin, vancomycin) were mostly added agents to initial antimicrobial therapy 141 (50.7%) episodes. Antifungal therapy consisting of fluconazole, liposomal amphotericin B, caspofungin, and voriconazole was used in addition to therapy in 97 (34.8%) of the episodes. A single agent was used in 82 (29.4%) episodes and combination therapy was used in 15 (5.4%) patients for antifungal treatment. Six patients had proven fungal infections. The mean duration of antibiotic use was 6.7 days for cefepime, 10.3 days for meropenem, 7.4 days for amikasin, 7.9 days for teicoplanin, 9.6 days for vancomycin, vancomycin 9.6, liposomal amphotericin B 8.6, caspofungin 8.9,

Table 1.
Characteristics of acute lymphoblastic leukemia patients with febrile neutropenia

Characteristics	Value
Median age (range)	7.2 (min: 1.1-max: 17.8) years
Sex (male/female)	81 (61.3%)/51 (%38.6) patients
Race (Turk/ Syrian/other)	116 (87.8%)/14 (10.6%)/2 (1.5%) patients
The risk group (SR/MR/HR)	37 (28%)/84 (63.6%)/11 (8.3%) patients
Relaps	10 (7.6%) patients

SR; Standart risk, MR; Medium risk, HR; High risk

Table 2.
Isolated pathogens in episodes with proven infectious etiology

	Blood	Urine	Total
Gram-positive organisms	54 (19.4%)	2 (0.7%)	56 (20.1%)
Coagulase-negative staphylococci (hominis, haemolyticus, epidermidis)	40 (19.4%)	-	-
Micrococcus luteus	5 (1.8%)	1 (0.36%)	-
Streptococcus viridans	3 (1.1%)	-	-
Enterococcus faecalis	5 (1.8%)	1 (0.36%)	-
Gram-negative organisms	25 (8.9%)	3 (1.1%)	28 (10%)
Escherichia coli	5 (1.8%)	2 (0.7%)	7 (%)
Klebsiella spp. (pneumonia, oxytoca)	5 (1.8%)	1 (0.36%)	6 (2.1%)
Pseudomonas spp. (aeruginosa, stutzeri)	3 (1.1%)	-	-
Serratia marcescens	2 (0.7%)	-	-
Acinetobacter spp. (baumannii, ursingii, junii, lwoffii)	5 (1.8%)	-	5 (1.8%)
Enterobacter cloacae	3 (1.1%)	-	-
Stenotrophomonas maltophilia	2 (0.7%)	-	-
Fungal organisms	5 (1.8%)	1 (0.36%)	6 (2.1%)
Candida spp. (albicans, tropicalis, krusei, lusitaniae)	5 (1.8%)	1 (0.36%)	6 (2.1%)
Polymicrobial	3 (1.1%)	-	3 (1.1%)
	86 (30.9%)	6 (2.1%)	92 (%33)

voriconazole 8.6 days. Colistin, ciprofloxacin, linezolid and trimethoprim-sulfamethoxazole in treatment dose were rarely used in febrile neutropenic patients. Acyclovir was started in 12 (4.3%) and oseltamivir was added to treatment in 15 (5.4%) of episodes (**Table 3**). SARS-CoV-2 was detected in 20 patients and no death occurred due to SARS-CoV-2 during the pandemic.

Of the 132 patients, a total of 4 (3%) died due to infection, 2 in induction and 2 in reduction phases. All deaths were due to pneumonia; two of them bacterial and acute respiratory distress syndrome, two of them fungal with radiological and laboratory findings of aspergillus and pulmonary hemorrhage. Granulocyte-colony stimulating factor were used only in 15 (5.4%) episodes after high-risk treatment protocols.

Discussion

Infection is the most important cause of morbidity and mortality during treatment in childhood ALL, particularly in developing countries. Improving outcomes are associated with improved risk stratification and supportive care. Persistent neutropenia is considered to be at particular risk for serious infectious complications and poorer outcomes in patients with FN.[10-12]

Table 3.
Use rates of antibiotics

	n (%)
Gram-negative	278 (100%)
Cefepime	65 (23.3%)
Cefepime + amicasin	27 (9.7%)
Meropenem	34 (12.2%)
Meropenem + amicasin	142 (51%)
Piperacillin/tazobactam	7 (2.5%)
Piperacillin/tazobactam + amicasin	3 (1.07%)
Other additional Gram-negative	15 (5.4%)
Ciprofloxacin	13 (4.6%)
Colistin	2 (0.7%)
Gram-positive	141 (50.7%)
Teicoplanin	120 (43.1%)
Vancomycin	20 (7.2%)
Linezolid	1 (0.35%)
Antifungal	97 (34.8%)
Fluconazole	24 (8.6%)
Liposomal amphotericin B	26 (9.3%)
Caspofungine	32 (11.5%)
Liposomal amphotericin B + *voriconasole*	8 (2.9%)
Caspofungin + *voriconasole*	7 (2.5%)
Antiviral	27 (9.7%)
Oseltamivir	15 (5.4%)
Acyclovir	12 (4.3%)
Anaerobic	6 (2.1%)
Metronidazole	6 (2.1%)
Others	10 (3.6%)
Clarithromycin	10 (3.6%)
Pneumocystis jirovecii	6 (2.1%)
Trimethoprim/sulfamethoxazole	6 (2.1%)

In our study, the median duration of neutropenia was 6.3 days (3-19 days) and the median ANC in FN episodes was 237/mm^3 (0-496/mm^3). In a study evaluating ALL and acute myeloid leukemia patients from Turkey, neutropenia's duration in ALL patients was found 6.69±3.84 days mean ANC 312±267/mm^3.[13]

In this study, we reported 92 (33%) causative infectious agents in FN episodes. In previous studies, proven microbiological infection was reported in 30-40% of cases and the frequency of isolation of specific organism varies among institutions.[13-20] Some studies have shown an increasing frequency of Gram-positive bacterial isolates, probably with multifactorial causes. Increased use of long-term indwelling central venous systems, intensive chemotherapy causing more severe mucositis, longer duration of neutropenia, use of H2 antagonists, and use of prophylactic antibacterial agents (fluoroquinolone and cotrimoxazole) may be important considerations.[13-17] We use central venous catheter routinely. Our study documented the predominance (20.1% of 33%) of Gram-positive organisms.

Identifying clinical or laboratory predictors of Gram-negative infection in FN patients with cancer is critical for early treatment. Immediate empiric broad-spectrum antimicrobial therapy is important to improve survival when the risk of bacteremia is predicted based on clinical and laboratory findings.[21-23] In case of septic shock findings such as fever rising with shirts, abnormal vital signs, hypotension, tachycardia, broad pulse pressure, mental status changes and respiratory dysfunction, an emergency treatment approach is carried out. (Supportive care of patients, replacement and close monitoring of fluid and electrolytes). If abdominal distension and pulmonary edema are present, we aimed to lower the threshold for albumin infusion to reduce intracellular edema.[24,25] Corticosteroids were used if shock findings persisted. No mortality was observed in any of the 20 patients who developed septic shock.

We prefer our patients to have combination therapy, meropenem plus amikacin therapy for FN treatment with much earlier addition of glycopeptides and antifungal therapy. If clinical stability is stable and fever is under control, we prefer to stop amikacin early.

Increased rates of fungal infections include advances in diagnostic methods, use of intensive chemotherapy drugs and steroids, long-term neutropenia, and use of broad-spectrum antibiotics and venous catheters.[26,27] The prevalence of IFI in children with only ALL patients ranges from 9.7%, 12.5%, 23%, 24% and the mortality rates were 4.2%, 4.2%, 9.5%, 13.3%, respectively.[19,28-30] In this study the proven and probable IFI incidence was higher (34.6%) and mortality rate was lower (1.5%). This may be because we have a low threshold for suspecting a "possible" fungal infection. Clinical criteria, host factors, imaging studies, and galactomannan levels used for the classification. Bronchoalveolar lavage was not performed in any of the patients.

The rate of infection-related mortality in current ALL studies is reported as 2-4% in developed countries and higher rates (20%) in developing countries.[31] All-cause mortality was 10.6% (n=14) and infection-related mortality was 3% (n=4) in this study. Two out of

4 died from acute respiratory distress syndrome due to bacterial pneumonia, and 2 out of 4 died from pulmonary hemorrhage due to fungal infection. As a new pediatric hematology and oncology center, three deaths occurred in the first 2 years and one death in the last 5 years in a 7-year period. Ten patients died of relapsed or refractory disease.

The limitation of this study is that we did not analyze the association between acute phase reactants and clinical manifestations and the severity of FN attacks.

Conclusion

Pediatric patients with ALL are offered a higher level of supportive care to better monitor and manage infectious complications. Close monitoring of patients, early initiation of empiric broad-spectrum antifungal therapy, and modifications in chemotherapy dosage based on bone marrow reserve improve survival and overall outcome. In our study, we showed that FN can be less fatal in ALL patients. For early and efficient treatment of FN, centers should evaluate their results for recognizing changing epidemiological patterns. Improving future outcomes in childhood ALL is related to reducing infection-related mortality.

Today, the solution that makes us pay the lowest price, spend the least time and money is the solution that makes us pay the highest price tomorrow. Tomorrow comes sooner than we expected. Although the books are guides, good observation and understanding of each patient's dynamics, which can be different, can increase the chances of success.

Ethical Approval: This retrospective study was approved by the Ethics Committee of Kayseri City Hospital (decision no: 643, date: 02.06.2022) and was performed in accordance with the ethical standards of the Declaration of Helsinki.

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Author Contributions: Karadoğan M: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Mutlu FT: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation, Writing.

Conflict of Interest: The authors have no conflicts of interest to declare.

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