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Antibiotic Escalation Within the First 72 Hours of Febrile Neutropenia: Association With Biomarkers and Clinical Outcomes

Nötropenik Ateşte İlk 72 Saat İçinde Antibiyotik Genişletmesi: Biyobelirteçler ve Klinik Sonuçlarla İlişki

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ABSTRACT

Aim: To determine the rate of antibiotic escalation within the first 72 hours of FN (Febrile neutropenia) episodes in pediatric patients and to evaluate the association of escalation with inflammatory biomarkers and clinical outcomes.
Methods: We retrospectively reviewed 84 FN episodes in children with malignancies treated between January 2017 and December 2021. Demographic and clinical data, initial and 72-hour antibiotic regimens, laboratory parameters (CRP, procalcitonin [PCT], interleukin-6 [IL-6], neutrophil-to-lymphocyte ratio [NLR]), blood culture results, length of hospital stay, and 30-day readmission were collected. Escalation was defined as a change to a broader-spectrum antibiotic within 72 hours. Logistic regression and comparative statistical tests were applied.
Results: Escalation occurred in 27% (23/84) of FN episodes, most frequently from piperacillin-tazobactam to meropenem. Patients requiring escalation had significantly higher median CRP (115 vs. 62 mg/L, p=0.01), PCT (1.3 vs. 0.5 ng/mL, p=0.02), and IL-6 (120 vs. 65 pg/mL, p=0.04) levels. Blood culture positivity was more common in the escalation group (52% vs. 23%, p=0.01). NLR was higher in escalation cases (8.2 vs. 5.6), with borderline statistical significance (p=0.06). Median length of hospital stay was longer in escalation patients (10 vs. 7 days, p=0.02). Thirty-day readmission did not differ significantly between groups.
Conclusions: Approximately one-quarter of FN episodes required antibiotic escalation within 72 hours. Elevated CRP, PCT, IL-6, and blood culture positivity were associated with escalation. These findings underscore the potential role of biomarkers in guiding early escalation decisions and optimizing antibiotic stewardship in pediatric FN.

Keywords: febrile neutropenia, antibiotic escalation, childhood malignancies, biomarkers

ÖZ

Amaç: Pediatrik hastalarda nötropenik ateş (FN) ataklarının ilk 72 saati içinde antibiyotik tedavisinin genişletilme oranını belirlemek ve bu genişletmenin inflamatuvar biyobelirteçler ile klinik sonuçlarla ilişkisini değerlendirmek.
Yöntemler: Ocak 2017–Aralık 2021 tarihleri arasında malignite tanılı çocuklarda görülen 84 FN atağı retrospektif olarak incelendi. Demografik ve klinik veriler, başlangıç ve 72. saatteki antibiyotik rejimleri, laboratuvar parametreleri (C-reaktif protein [CRP], prokalsitonin [PCT], interlökin-6 [IL-6], nötrofil/lenfosit oranı [NLR]), kan kültürü sonuçları, hastanede yatış süresi ve 30 günlük yeniden yatış oranları kaydedildi. Antibiyotik genişletmesi, 72 saat içinde daha geniş spektrumlu bir antibiyotiğe geçiş olarak tanımlandı. Lojistik regresyon ve karşılaştırmalı istatistiksel analizler uygulandı.
Bulgular: FN ataklarının %27'sinde (23/84) antibiyotik tedavisinde genişletme yapıldı ve en sık piperasilin-tazobaktamdan meropeneme geçiş gerçekleştirildi. Antibiyotik genişletmesi yapılan hastalarda median CRP (115'e karşı 62 mg/L, p=0,01), PCT (1.3'e karşı 0,5 ng/mL, p=0,02) ve IL-6 (120'ye karşı 65 pg/mL, p=0,04) düzeyleri anlamlı derecede yüksekti. Kan kültürü pozitifliği genişletme grubunda daha sık görüldü (%52'ye karşı %23, p=0,01). NLR değerleri de daha yüksek saptandı (8,2'ye karşı 5,6, p=0,06). Antibiyotik genişletmesi yapılan hastalarda ortanca yatış süresi daha uzundu (10'a karşı 7 gün, p=0,02). Otuz günlük yeniden yatış oranlarında anlamlı fark bulunmadı.
Sonuç: FN ataklarının yaklaşık dörtte birinde ilk 72 saat içinde antibiyotik tedavisinin genişletilmesi gerekmiştir. Yüksek CRP, PCT, IL-6 düzeyleri ve kan kültürü pozitifliği antibiyotik genişletmesi ile ilişkili bulunmuştur. Bu bulgular, biyobelirteçlerin erken antibiyotik genişletme kararlarını yönlendirmede ve pediatrik FN'de akılcı antibiyotik kullanımının optimize edilmesinde potansiyel bir rol oynayabileceğini göstermektedir.

Anahtar Kelimeler: nötropenik ateş, antibiyotik genişletmesi, çocukluk çağı maligniteleri, biyobelirteçler

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Introduction

Febrile neutropenia (FN) is one of the most common oncologic emergencies in pediatric oncology practice and remains a major cause of morbidity and mortality. In patients receiving cytotoxic chemotherapy, the reduction in neutrophil counts markedly weakens the immune response against infectious agents. As a result, FN episodes can lead to rapid clinical deterioration, and each hour in initiating treatment is of critical importance [1,2]. Current international and national guidelines recommend the initiation of broad-spectrum antibiotics at first evaluation, with carbapenems or piperacillin-tazobactam as preferred regimens, particularly in the presence of hemodynamic instability or high-risk clinical features [3,4].

However, the global rise in antimicrobial resistance necessitates caution in empirical treatment strategies. To prevent resistance development, limit unnecessary use of broad-spectrum agents, and ensure cost-effectiveness, antimicrobial stewardship programs have become increasingly important [5]. In this context, alongside the "de-escalation" approach from broad to narrow therapy, a rational and evidence-based application of "escalation" strategies—guided by clinical and laboratory data—has also become critical [6]. In particular, in cases initially treated with agents such as piperacillin-tazobactam, the need to switch to meropenem or even broader regimens often arises in the presence of clinical deterioration or positive culture results [7].

In this decision-making process, several biomarkers may provide valuable support. C-reactive protein (CRP) and procalcitonin (PCT) have long been used as early indicators of bacterial infection, while in recent years interleukin-6 (IL-6) and the neutrophil-to-lymphocyte ratio (NLR) have been investigated for their prognostic value [8-10]. In the literature, PCT and IL-6 have been shown to be strongly associated with bacteremia and sepsis, whereas NLR has been reported to correlate with infection risk in patients with hematologic malignancies [11]. Nevertheless, data on the contribution of these biomarkers to antibiotic escalation decisions in FN remain limited.

The present study aims to determine the rate of antibiotic escalation within the first 72 hours of FN episodes and to evaluate the association of this decision with biomarkers such as CRP, PCT, IL-6, and NLR, as well as blood culture results. In addition, the effects of escalation on hospital length of stay and readmission rates will be examined. This approach is expected to contribute to more predictable and evidence-based antimicrobial stewardship strategies in clinical practice.

Methods

This study was designed as a single-center, retrospective investigation. It included patients who presented with febrile neutropenia (FN) and were hospitalized in the pediatric hematology-oncology clinic between January 2017 and December 2021. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Children with hematologic malignancies or solid tumors who developed chemotherapy-induced neutropenia and met the diagnostic criteria for FN—defined as a single temperature measurement ≥38.0 °C or persistent fever ≥37.5 °C for at least 1 hour—were eligible for inclusion [12,13]. The inclusion criteria were: age 0–18 years, chemotherapy-induced absolute neutrophil count (ANC) <500/mm³ or expected to fall below 500/mm³ within 48 hours, hospitalization for FN, initial antibiotic therapy with either piperacillin-tazobactam or meropenem, and complete documentation of initial and 72-hour antibiotic regimens in the medical records. Exclusion criteria were: prior allogeneic hematopoietic stem cell transplantation, receipt of antibiotics at another center before initiation of therapy, incomplete laboratory or clinical data, or death within the first 24 hours due to mortality. The demographic and clinical characteristics of the study population are summarized in Table 1.

Antibiotic escalation was defined by comparing the spectrum score of the initial antibiotic with that of the regimen at 72 hours. Initial antibiotic regimens and subsequent changes at 72 hours are presented in Table 1. Spectrum scoring was based on literature-adapted categories, ranked from narrower to broader coverage: cephalosporins (1–2), piperacillin-tazobactam/cefepime (3), carbapenems (4), and regimens including glycopeptides or colistin (5) [14-16].

A switch to a higher score regimen at 72 hours was considered escalation. Blood cultures were classified as positive in the presence of bacterial growth, whereas single-bottle coagulase-negative staphylococci, suspected to represent contamination, were excluded from analysis. Biomarkers were recorded as follows: CRP (mg/L) measured by standard laboratory methods, PCT (ng/mL) assessed by electrochemiluminescence assay, IL-6 measured by ELISA when available, and NLR (neutrophil-to-lymphocyte ratio) calculated automatically from complete blood count parameters.

Table 1. Demographic and Clinical Properties and Initial Antibiotic Regime with Changes at 72nd hour

Age (years), median (min–max)	7 (2–16)
Male Gender, n (%)	46 (55%)
Diagnosis: ALL	39 (46%)
Diagnosis: AML	18 (21%)
Diagnosis: Solid tumor	27 (33%)
Antibiotic regime	
Initial piperacilin-tazobactam	51 (61%)
Initial meropenem	33 (39%)
Patients with escalation at 72nd hour	23 (27%)
Patients without escalation at 72nd hour	61 (73%)

The following data were extracted from patient files: age, sex, underlying malignancy, number of FN episodes, baseline complete blood count (ANC, lymphocyte count, hemoglobin, platelet count), biochemical and inflammatory markers (CRP, PCT, IL-6), blood culture results, initial antibiotic regimen, antibiotic regimen at 72 hours, hospital length of stay (LOS, days), and readmission within 30 days after discharge. The primary endpoint was antibiotic escalation (yes/no) within the first 72 hours. Secondary endpoints included hospital LOS (days) and 30-day readmission rates.

Statistical Analysis: Statistical analyses were performed using IBM SPSS Statistics v25.0 (IBM Corp., Armonk, NY) and R v4.2 software. Continuous variables were expressed as mean ± SD or median (minimum–maximum), while categorical variables were reported as frequencies and percentages. The Shapiro–Wilk test was used to assess normality of continuous variables. Student's t-test was applied for normally distributed variables, and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square or Fisher's exact test. Logistic regression analysis was conducted to identify independent risk factors associated with escalation. The dependent variable was escalation (yes/no); independent variables included CRP, PCT, IL-6, NLR, and culture positivity. The model was adjusted for clinical covariates such as age and diagnosis. Effect sizes were reported as odds ratios (OR) with 95% confidence intervals (CI). The relationship between escalation and hospital LOS was also analyzed, with group comparisons performed for both mean and median LOS values. A p-value <0.05 was considered statistically significant. All patient data were anonymized prior to analysis.

Results

A total of 84 febrile neutropenia (FN) episodes were included in the study. The median age of patients was 7 years (range: 2–16 years), and 55% of the cohort were male. The most common underlying malignancy was acute lymphoblastic leukemia (46%), followed by acute myeloid leukemia (21%) and solid tumors (33%).

At presentation, all patients received empirical antibiotic therapy. Piperacillin-tazobactam was the initial treatment in 61% (n=51) of episodes, while meropenem was used in 39% (n=33). Escalation of antibiotic therapy within the first 72 hours was observed in 27% of FN episodes (n=23/84). The most frequent escalation occurred in patients initially started on piperacillin-tazobactam, where clinical deterioration necessitated a switch to meropenem.

Biomarkers: Baseline CRP levels were significantly higher in the escalation group compared to the non-escalation group (median 115 mg/L, IQR 82–146 vs. 62 mg/L, IQR 38–95; p=0.01). Similarly, PCT values were markedly elevated in the escalation group (median 1.3 ng/mL, IQR 0.8–2.0 vs. 0.5 ng/mL, IQR 0.2–0.9; p=0.02). Among the 40 patients with available IL-6 measurements, median IL-6 levels were higher in the escalation group (120 pg/mL) compared to the non-escalation group (65 pg/mL; p=0.04). The neutrophil-to-lymphocyte ratio (NLR) was also greater in patients who underwent escalation [median 8.2 (IQR 6.4–11.5)] compared with those who did not [median 5.6 (IQR 3.8–7.9)];

this difference was borderline significant (p=0.06). Comparative biomarker levels between groups are presented in Table 2.

Table 2. Correlation of Biomarkers With Escalation and Clinical Results

		With Escalation	Without Escalation	p value
Biomarker	CRP (mg/L), median (IQR)	115 (82–146)	62 (38–95)	0.01
	PCT (ng/mL), median (IQR)	1.3 (0.8–2.0)	0.5 (0.2–0.9)	0.02
	IL-6 (pg/mL), median (IQR)	120 (80–170)	65 (40–100)	0.04
	NLR, median (IQR)	8.2 (6.4–11.5)	5.6 (3.8–7.9)	0.06
	Result			
	Positive blood culture, n (%)	12 (52%)	14 (23%)	0.01
	Hospitalization, median days (IQR)	10 (8–13)	7 (6–9)	0.02
	Rehospitalization in 30 days, n (%)	5 (22%)	8 (14%)	0.41

Blood culture results: Overall, 31% (n=26) of FN episodes yielded positive blood cultures. Culture positivity was more frequent in the escalation group (52%) compared with the non-escalation group (23%) (p=0.01). Gram-negative bacilli were the predominant isolates, primarily Escherichia coli (38%) and Klebsiella pneumoniae (27%). Among Gram-positive organisms, coagulase-negative staphylococci (19%) and Enterococcus spp. (8%) were most commonly identified. Clinical outcomes are summarized in Table 2.

Length of stay: The median hospital length of stay was significantly longer in the escalation group [10 days (IQR 8–13)] compared with the non-escalation group [7 days (IQR 6–9)] (Mann–Whitney U test, p=0.02).

Readmission: Within 30 days after discharge, readmission occurred in 22% (n=5) of patients in the escalation group and 14% (n=8) of those in the non-escalation group; this difference was not statistically significant (p=0.41).

In summary, approximately one-quarter of FN episodes required antibiotic escalation within the first 72 hours. Elevated CRP, PCT, and IL-6 levels, as well as culture positivity, were significantly associated with escalation. Furthermore, patients who required escalation had a markedly longer hospital stay.

Discussion

In this study, approximately one-quarter of febrile neutropenia (FN) episodes in pediatric patients undergoing treatment for malignancy required antibiotic escalation within the first 72 hours. Our findings demonstrated that elevated CRP, PCT, and IL-6 levels, as well as positive blood cultures, emerged as significant predictors of escalation. Furthermore, patients who underwent escalation had a significantly longer hospital stay. These results underscore the importance of incorporating biomarkers into early clinical decision-making for antibiotic management in FN.

The use of broad-spectrum regimens as initial empirical therapy in FN remains the cornerstone of both national and international guidelines [3,16]. However, subsequent reassessment of antibiotic therapy in light of clinical and microbiological findings is strongly recommended. Traditionally, this approach has been framed around de-escalation strategies, i.e., narrowing coverage once the clinical situation stabilizes. In recent years, however, rising rates of resistant Gram-negative bacteria and the risk of rapid clinical deterioration in high-risk patients have highlighted the necessity of early escalation strategies as well [6,7]. In our study, the escalation rate was 27%, which aligns with the 20–35% range reported in the literature [12,13].

The use of biomarkers to guide antibiotic management in FN has been a subject of investigation for decades. CRP remains one of the most widely used and readily available markers. Our finding that CRP levels were higher in the escalation group suggests that CRP may help predict the need for more intensive therapy. Nevertheless, CRP is known to have limited specificity, as elevations may occur in a variety of inflammatory conditions [8]. By contrast, PCT has emerged as a more reliable marker of sepsis in recent years. In our cohort, PCT levels were significantly elevated among patients who required escalation. Previous studies have shown that PCT strongly predicts bacteremia and may guide both shortening and intensification of antibiotic therapy [9,10].

IL-6, a cytokine that responds very early to infection, has been reported in some studies to predict FN outcomes earlier than CRP and PCT. The association between IL-6 and escalation in our study supports these observations. However, the limited availability of IL-6 testing in routine practice restricts its broader clinical utility [9]. The neutrophil-to-lymphocyte ratio (NLR) has gained increasing attention as a prognostic marker of sepsis and infection, and has also been linked to infection risk in patients with hematologic malignancies. In our study, NLR was higher in the escalation group but reached only borderline significance, highlighting the need for larger, prospective studies to clarify its role [11].

Blood culture positivity emerged as one of the strongest determinants of antibiotic escalation. In our study, culture positivity was significantly more frequent in the escalation group. Gram-negative pathogens, particularly Escherichia coli and Klebsiella pneumoniae, were closely associated with early clinical deterioration, often making escalation unavoidable. Similarly, the literature has reported markedly higher rates of early escalation in culture-positive FN cases dominated by Gram-negative organisms [14,15].

The longer hospital stay observed among patients who required escalation is consistent with expectations and indicates that escalation typically reflects more severe clinical courses. Previous studies have also reported that escalation is associated with significantly prolonged hospitalization, which imposes additional burdens on both patient quality of life and healthcare system costs [6,7]. On the other hand, the absence of a significant difference in 30-day readmission rates between groups suggests that the long-term impact of escalation on post-discharge outcomes may be limited.

Limitations: This study has several limitations. First, its retrospective and single-center design may limit generalizability. Second, IL-6 measurements were not available for all patients, reducing sample size for this analysis. Finally, escalation decisions were dependent on clinician judgment, which may introduce heterogeneity.

Conclusions

Our study demonstrated that antibiotic escalation was required in approximately one-quarter of FN episodes, with elevated CRP, PCT, IL-6 levels, and culture positivity serving as valuable predictors of escalation. These findings may support the integration of biomarkers into FN management and contribute to the development of more effective antimicrobial stewardship programs. Prospective, multicenter studies with larger cohorts are warranted to further elucidate the impact of escalation strategies on patient survival, antimicrobial resistance, and healthcare costs.

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