

Clinical Phenotypes and Glycopeptide Escalation Patterns in Pediatric Febrile Neutropenia: Associations with Short-Term Outcomes and Acute Kidney Injury Risk

Pediyatrik Febril Nötropenide Klinik Fenotipler ve Glikopeptid Eskalasyon Paternleri: Kısa Dönem Sonuçlar ve Akut Böbrek Hasarı Riski ile İlişkisi

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Abstract

Objective: Febrile neutropenia (FN) in pediatric oncology is a clinically heterogeneous syndrome in which early antibiotic escalation decisions are frequently driven by non-specific severity cues. We aimed to identify baseline clinical phenotypes of pediatric FN, to describe early glycopeptide escalation patterns across these phenotypes, and to examine their associations with short-term outcomes and acute kidney injury (AKI).

Materials and Methods: We conducted a retrospective cohort study including 106 FN episodes experienced by 82 pediatric oncology patients initially treated with piperacillin-tazobactam monotherapy. Baseline clinical and laboratory variables available within the first 6 hours of FN onset were used for unsupervised k-means clustering to derive latent clinical phenotypes. Early glycopeptide escalation was defined as the initiation of vancomycin or teicoplanin within 48 hours. Associations with clinical outcomes on day 7 and AKI were evaluated using multivariable cluster-robust regression and inverse probability of treatment weighting.

Results: Three distinct FN phenotypes were identified: a high-inflammatory/mucositis-dominant phenotype (39.6%), a hemodynamically severe phenotype (22.6%), and a lower-severity phenotype (37.7%). Early glycopeptide escalation occurred in 26.4% of episodes and was disproportionately concentrated in the high-inflammatory and hemodynamically severe phenotypes. AKI developed in 10.4% of FN episodes and clustered predominantly within escalation-prone phenotypes. After adjustment, early escalation was not associated with improved day-7 clinical success but was associated with a higher observed risk of AKI.

Conclusion: Pediatric FN comprises distinct clinical phenotypes that differentially drive antibiotic escalation behavior and renal injury risk. A phenotype-informed approach may help to optimize escalation

Öz

Amaç: Pediyatrik onkolojide febril nötropeni (FN), erken antibiyotik eskalasyon kararlarının sıklıkla özgül olmayan klinik şiddet göstergelerine dayandığı, klinik olarak heterojen bir sendromdur. Bu çalışmada pediyatrik FN için başlangıç klinik fenotiplerinin tanımlanması, bu fenotipler arasında erken glikopeptid eskalasyon paternlerinin ortaya konması ve kısa dönem klinik sonuçlar ile akut böbrek hasarı (ABH) ile ilişkilerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif kohort çalışmaya, başlangıç tedavisi olarak piperasilin-tazobaktam monoterapisi alan 82 pediyatrik onkoloji hastasında gözlenen 106 FN atağı dahil edildi. FN başlangıcından sonraki ilk 6 saat içinde elde edilen klinik ve laboratuvar değişkenleri kullanılarak denetimsiz k-means kümeleme yöntemi ile gizil klinik fenotipler belirlendi. Erken glikopeptid eskalasyonu, FN başlangıcından sonraki 48 saat içinde vankomisin veya teikoplanin başlanması olarak tanımlandı. Yedinci gün klinik sonuçlar ve ABH ile ilişkiler, küme-dayanıklı çok değişkenli regresyon ve ters olasılık ağırlıklandırması yöntemleri kullanılarak analiz edildi.

Bulgular: Üç farklı FN fenotipi tanımlandı: Yüksek enflamasyon/mukozit baskın fenotip (%39,6), hemodinamik olarak ağır fenotip (%22,6) ve düşük şiddetli fenotip (%37,7). Erken glikopeptid eskalasyonu atakların %26,4'ünde gözlemlendi ve ağırlıklı olarak yüksek enflamasyonlu ve hemodinamik olarak ağır fenotiplerde yoğunlaştı. ABH FN ataklarının %10,4'ünde gelişti ve büyük ölçüde eskalasyona eğilimli fenotiplerde kümelendi. Düzeltilmiş analizlerde erken glikopeptid eskalasyonu, 7. gün klinik başarı ile ilişkili bulunmazken, ABH gelişme riskinde gözlenen artış ile ilişkiliydi.

Sonuç: Pediyatrik FN, antibiyotik eskalasyon davranışı ve renal hasar riskini farklı biçimlerde yönlendiren belirgin klinik fenotiplerden oluşmaktadır. Fenotip temelli bir yaklaşım, pediyatrik hematoloji-



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Abstract

decisions and potentially reduce preventable toxicity. However, given the observational design of this study, these associations should be interpreted with caution.

Keywords: Febrile neutropenia, Pediatric oncology, Glycopeptide antibiotics, Antimicrobial stewardship, Clinical phenotypes, Acute kidney injury, Nephrotoxicity

Öz

onkoloji pratiğinde eskalasyon kararlarının daha rasyonel hale getirilmesine ve önlenabilir toksisitenin potansiyel olarak azaltılmasına katkı sağlayabilir. Bununla birlikte, gözlemsel çalışma tasarımı nedeniyle bu ilişkiler dikkatli yorumlanmalıdır.

Anahtar Sözcükler: Febril nötrojeni, Pediatrik onkoloji, Gikopektid antibiyotikler, Antimikrobiyal yönetim, Klinik fenotipler, Akut böbrek hasarı, Nefrotoksisite

Introduction

Febrile neutropenia (FN) remains one of the most frequent and potentially life-threatening complications in pediatric oncology, particularly among children receiving intensive chemotherapy for acute lymphoblastic leukemia and other hematological malignancies [1,2,3]. Although empiric broad-spectrum antibacterial therapy has substantially reduced infection-related mortality, the optimal strategy for antimicrobial escalation during the early course of FN remains uncertain [4,5,6].

Current international guidelines recommend reserving glycopeptide antibiotics for narrowly defined indications including hemodynamic instability, suspected catheter-related infection, radiologically confirmed pneumonia, or microbiologically documented gram-positive bloodstream infection [4,5,6]. Despite these recommendations, observational studies consistently demonstrate substantial clinical overuse of glycopeptides during pediatric FN, often initiated in the absence of guideline-supported triggers [7,8,9,10,11,12]. Escalation decisions are frequently driven by non-specific severity cues such as persistent fever, rising inflammatory markers, mucositis, or evolving clinical concern for sepsis rather than pathogen-directed evidence [10,11,12,13,14,15]. This pattern raises important concerns regarding antimicrobial stewardship and unintended downstream harms.

One of the most clinically consequential adverse effects associated with glycopeptide exposure is acute kidney injury (AKI), particularly in pediatric oncology populations characterized by repeated antimicrobial exposures, concurrent nephrotoxic agents, and baseline physiological vulnerability [16,17,18,19,20,21,22,23,24,25]. Both vancomycin and teicoplanin have been implicated in nephrotoxicity, with the risk amplified by inflammatory burden, critical illness, and combination therapy with antipseudomonal β -lactams [20,21,22,23,24,25]. Although multiple studies and meta-analyses have shown that early glycopeptide escalation does not confer short-term clinical benefit in unselected FN populations [7,8,9,13,14,15], it remains unclear whether renal toxicity risk is uniformly distributed across FN episodes or instead concentrates within specific clinical contexts. Disentangling the relative contributions of drug exposure and underlying clinical severity to renal injury remains challenging in observational settings.

Importantly, pediatric FN is not a biologically or clinically homogeneous syndrome. Unsupervised phenotyping approaches in other critical care syndromes have identified latent clinical subgroups with distinct trajectories, treatment responses, and toxicity profiles [22,23,24]. In pediatric FN, however, such phenotype-based frameworks remain underexplored and existing escalation studies have largely relied on average treatment effects.

We hypothesized that early glycopeptide escalation during pediatric FN represents a clinician-driven behavioral response embedded within a heterogeneous clinical syndrome. Specifically, we assumed that distinct FN phenotypes could be identified using baseline clinical and laboratory variables, that escalation behavior would disproportionately cluster within certain phenotypic subgroups, and that renal toxicity signals would concentrate within escalation-prone phenotypes.

Accordingly, the objectives of this study were to identify latent clinical phenotypes of pediatric FN using unsupervised clustering of baseline severity and inflammatory variables, to characterize how these phenotypes drive early glycopeptide escalation behavior, and to examine whether AKI preferentially clusters within specific phenotypic subgroups.

Materials and Methods

We conducted a retrospective cohort study of pediatric oncology patients who experienced FN episodes between January 2023 and January 2026 at a tertiary referral center. FN was defined as a single oral temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38.0 °C for ≥ 1 hour in the setting of an absolute neutrophil count (ANC) of < 500 cells/ μ L or an expected decline to < 500 cells/ μ L within 48 hours.

Episodes were eligible for inclusion if the patients were initially managed with empiric piperacillin-tazobactam monotherapy at FN onset in accordance with institutional protocols. Episodes involving documented hemodynamic instability or septic shock at FN presentation were excluded to minimize baseline severity heterogeneity. FN episodes occurring during intensive care unit admission or with microbiologically confirmed gram-positive bloodstream infection at presentation were also excluded to focus on escalation decisions arising under diagnostic uncertainty.

The study protocol was approved by the University of Health Sciences Türkiye, İzmir City Hospital Non-Interventional Ethics Committee (decision date: 17.12.2025; decision no: 2025/556), and the requirement for informed consent was waived due to the retrospective design of the study.

Clinical, laboratory, and treatment data were obtained and abstracted from electronic medical records by two independent investigators using a standardized data collection form. Discrepancies were resolved by consensus review. Baseline variables were defined as those available within the first 6 hours of FN onset and included age, sex, malignancy type, ANC, C-reactive protein (CRP), presence of grade ≥ 3 mucositis, suspected sepsis or pulmonary infection, and concomitant nephrotoxic exposures. Nephrotoxic co-exposures included aminoglycosides, amphotericin B, non-steroidal anti-inflammatory drugs, and intravenous contrast administered within 48 hours of FN onset. Baseline creatinine was defined as the most recent serum creatinine value obtained within 7 days prior to FN onset.

Variables reflecting early clinical deterioration, including typhilitis and septic shock, were defined as events occurring within the first 48 hours after FN onset and were not used as clustering inputs but were examined for phenotype characterization and outcome associations.

Early glycopeptide escalation was defined as the initiation of teicoplanin or vancomycin within 48 hours of FN onset. Agent selection (teicoplanin versus vancomycin) and duration of glycopeptide exposure were recorded. The temporal relationship between glycopeptide initiation and the onset of AKI could not be precisely determined due to the study's retrospective design. In addition, detailed data on glycopeptide dose adjustments or discontinuation following changes in renal function were not systematically available. Clinical success on day 7 was defined as defervescence and clinical stability without further antimicrobial escalation, intensive care unit admission, or death within 7 days of FN onset.

AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria as an increase in serum creatinine ≥ 1.5 times the baseline value within 7 days of FN onset. The peak creatinine ratio was defined as peak serum creatinine divided by baseline creatinine.

Statistical Analysis

Unsupervised clustering was performed using standardized baseline clinical and laboratory variables, including CRP, ANC, grade ≥ 3 mucositis, suspected sepsis, suspected pulmonary infection, malignancy type, and nephrotoxic co-exposures. Continuous variables were standardized to z-scores and categorical variables were encoded as binaries prior to clustering to enable the integration of mixed data types.

We applied k-means clustering to derive latent clinical phenotypes. The optimal number of clusters (k) was selected based on silhouette coefficient maximization and clinical interpretability, balancing model parsimony with biological plausibility. Cluster robustness was assessed through repeated random subsampling, with the concordance of cluster assignments evaluated across resampled datasets. Phenotypes were labeled post hoc based on dominant clinical features and the relative burden of inflammatory, mucosal, and severity-related variables.

Continuous variables were summarized as median and interquartile range (IQR) values and categorical variables as numbers and percentages. Comparisons across phenotypes were performed using the Kruskal-Wallis test for continuous variables and the chi-square or Fisher exact test for categorical variables, as appropriate.

Because multiple FN episodes could occur for a single patient, cluster-robust standard errors were used to account for within-patient correlation and repeated-measures dependency. Multivariable logistic regression was used to identify independent predictors of early glycopeptide escalation. Covariates were selected a priori based on clinical plausibility and a literature review rather than automated variable selection procedures.

To mitigate the confounding by indication inherent to clinician-driven escalation decisions, we applied propensity score-based inverse probability of treatment weighting (IPTW). The propensity score model incorporated baseline variables plausibly associated with escalation behavior, including CRP, ANC, mucositis, suspected sepsis, suspected pulmonary infection, malignancy type, and nephrotoxic co-exposures. Covariate balance before and after weighting was assessed using standardized mean differences. Weighted regression models were used to estimate associations between early glycopeptide escalation and clinical outcomes and AKI.

Sensitivity analyses included unweighted multivariable models and phenotype-stratified outcome analyses to assess the robustness of effect estimates.

All statistical analyses were performed using R software (R Foundation, Vienna, Austria). Two-sided values of $p < 0.05$ were considered statistically significant.

Results

A total of 106 FN episodes occurring in 82 pediatric oncology patients were included in the analysis. The median age was 8.6 years (IQR: 4.1-13.2) and 46 patients (56.1%) were male. Acute lymphoblastic leukemia accounted for 48 FN episodes (45.3%). All episodes were initially managed with piperacillin-tazobactam monotherapy at FN onset.

Unsupervised clustering of standardized baseline variables identified three distinct clinical phenotypes (Figure 1). Baseline demographic, clinical, and laboratory characteristics stratified by phenotype are summarized in Table 1.

Phenotype 1 (high-inflammatory/mucositis-dominant) accounted for 42 FN episodes (39.6%) and was characterized by

elevated baseline CRP levels, frequent grade ≥3 mucositis, and higher rates of suspected sepsis. Phenotype 2 (hemodynamically severe) accounted for 24 FN episodes (22.6%) and was marked by early clinical deterioration, including typhlitis and septic shock occurring within the first 48 hours. Phenotype 3 (lower severity) accounted for 40 FN episodes (37.7%) and exhibited a uniformly lower inflammatory burden and fewer severity-related features.

Phenotype Profiles Based on Standardized Baseline Variables

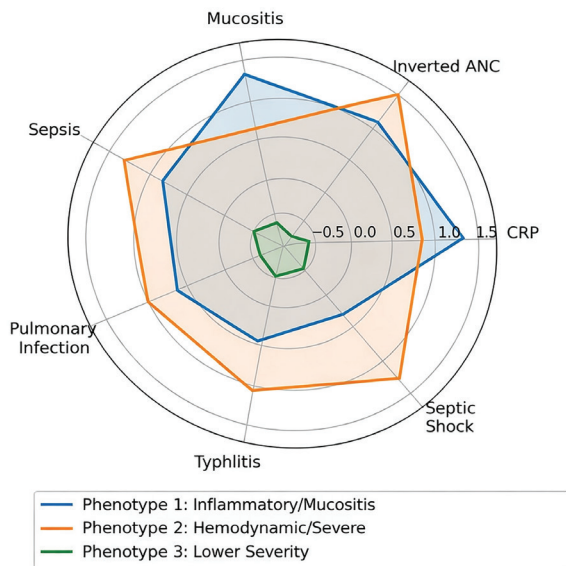


Figure 1. Heatmap of standardized baseline clinical and laboratory variables used to derive three clinical phenotypes of pediatric febrile neutropenia. Variables included C-reactive protein (CRP), absolute neutrophil count (ANC), grade ≥3 mucositis, suspected sepsis or pulmonary infection, malignancy type, and nephrotoxic co-exposures.

Early glycopeptide escalation occurred in 28 of 106 FN episodes (26.4%), including teicoplanin in 20 (71.4%) and vancomycin in 8 (28.6%). Escalation rates differed markedly across the phenotypes (Table 2), with escalation occurring in 16 of 42 episodes (38.1%) of phenotype 1, 10 of 24 episodes (41.7%) of phenotype 2, and 2 of 40 episodes (5.0%) of phenotype 3 (p<0.001).

Vancomycin use was disproportionately concentrated within cases of phenotype 2, accounting for 6 of 8 vancomycin initiations (75.0%), whereas teicoplanin predominated in phenotype 1 (14 of 20, 70.0%) (Table 2).

In multivariable cluster-robust logistic regression, elevated baseline CRP (adjusted odds ratio [aOR]: 1.28 per 10 mg/L increase; 95% confidence interval [CI]: 1.12-1.46), grade ≥3 mucositis (aOR: 3.41; 95% CI: 1.44-8.06), and suspected sepsis or pulmonary infection (aOR: 2.76; 95% CI: 1.18-6.45) were independently associated with early glycopeptide escalation (Table 2).

AKI occurred in 11 of 106 FN episodes (10.4%). These events were unevenly distributed across phenotypes (Table 3), occurring in 5 of 42 episodes (11.9%) of phenotype 1, 5 of 24 episodes (20.8%) of phenotype 2, and 1 of 40 episodes (2.5%) of phenotype 3 (p=0.03).

Table 1. Baseline characteristics of febrile neutropenia episodes by clinical phenotype.

Characteristic	Overall (n=106)	Phenotype 1: high-inflammatory/mucositis-dominant (n=42)	Phenotype 2: hemodynamically severe (n=24)	Phenotype 3: lower severity (n=40)	p
Age, years, median (IQR)	8.6 (4.1-13.2)	8.2 (4.0-12.8)	9.4 (4.6-13.9)	8.3 (3.9-13.1)	0.78
Male sex, n (%)	46 (56.1)	24 (57.1)	14 (58.3)	18 (45.0)	0.44
Acute lymphoblastic leukemia, n (%)	48 (45.3)	20 (47.6)	12 (50.0)	16 (40.0)	0.71
Absolute neutrophil count, cells/μL, median (IQR)	120 (30-280)	90 (20-210)	140 (40-310)	160 (60-340)	0.04
C-reactive protein, mg/L, median (IQR)	38 (14-92)	78 (42-148)	46 (22-96)	18 (6-36)	<0.001
Grade ≥3 mucositis, n (%)	28 (26.4)	18 (42.9)	6 (25.0)	4 (10.0)	0.002
Suspected sepsis, n (%)	31 (29.2)	16 (38.1)	11 (45.8)	4 (10.0)	0.001
Suspected pulmonary infection, n (%)	22 (20.8)	10 (23.8)	8 (33.3)	4 (10.0)	0.04
Nephrotoxic co-exposures*, n (%)	29 (27.4)	14 (33.3)	9 (37.5)	6 (15.0)	0.04
Baseline creatinine, mg/dL, median (IQR)	0.42 (0.30-0.58)	0.41 (0.29-0.55)	0.44 (0.32-0.61)	0.40 (0.28-0.56)	0.66

Values are presented as median (interquartile range) or number (percentage).

*: Nephrotoxic exposures included aminoglycosides, amphotericin B formulations, contrast media, and concurrent nephrotoxic chemotherapeutic agents; IQR: interquartile range.

AKI was observed to cluster disproportionately within escalation-prone phenotypes, accounting for 10 of 11 AKI events (90.9%). Median peak creatinine ratios were higher in cases of phenotypes 1 and 2 compared to phenotype 3 (Table 3). The temporal trajectories of serum creatinine ratios by phenotype are shown in Figure 2, demonstrating more pronounced and sustained creatinine elevations in escalation-prone phenotypes. However, the temporal relationship between glycopeptide initiation and AKI onset could not be definitively established with the available dataset. These findings should be interpreted as associative rather than causal due to the observational design.

In IPTW-weighted analyses, early glycopeptide escalation was not associated with improved day-7 clinical success (weighted OR: 0.92; 95% CI: 0.41-2.08; p=0.84). However, early escalation was associated with a higher observed risk of AKI (weighted OR: 2.87; 95% CI: 1.08-7.61; p=0.035). The results were consistent across unweighted multivariable models and phenotype-stratified sensitivity analyses.

Discussion

In this retrospective cohort study, we applied an unsupervised phenotyping framework to pediatric FN and demonstrated that early glycopeptide escalation is not a uniform therapeutic intervention. Rather, it is a phenotype-driven clinician behavior embedded within a heterogeneous clinical syndrome. Three distinct clinical phenotypes were identified, each characterized by unique severity profiles, escalation propensities, and renal safety signals. Importantly, renal toxicity was not uniformly distributed across FN episodes; it clustered disproportionately within escalation-prone phenotypes without accompanying short-term clinical benefit. This reframes early glycopeptide escalation from a purely therapeutic act into a context-dependent behavioral response to clinical uncertainty. This study was not designed to evaluate dose-dependent antimicrobial efficacy or the pharmacokinetic safety of glycopeptides. Instead, it focuses on real-world escalation behavior and its association with renal injury within a heterogeneous pediatric hematology population. The absence of systematic therapeutic drug monitoring reflects

Table 2. Early glycopeptide escalation and independent predictors.

Variable	Overall (n=106)	Early glycopeptide escalation (n=28)	No escalation (n=78)	p	Adjusted OR (95% CI)*	p
Phenotype 1, n (%)	42 (39.6)	16 (57.1)	26 (33.3)	0.02	2.18 (0.84-5.64)	0.11
Phenotype 2, n (%)	24 (22.6)	10 (35.7)	14 (17.9)	0.04	2.64 (0.96-7.29)	0.06
Phenotype 3, n (%)	40 (37.7)	2 (7.1)	38 (48.7)	<0.001	Reference	-
C-reactive protein per 10 mg/L, median (IQR)	38 (14-92)	92 (54-156)	26 (10-64)	<0.001	1.28 (1.12-1.46)	0.001
Grade ≥3 mucositis, n (%)	28 (26.4)	14 (50.0)	14 (17.9)	<0.001	3.41 (1.44-8.06)	0.005
Suspected sepsis or pulmonary infection, n (%)	43 (40.6)	19 (67.9)	24 (30.8)	<0.001	2.76 (1.18-6.45)	0.02
Absolute neutrophil count, cells/μL, median (IQR)	120 (30-280)	90 (20-210)	140 (40-310)	0.04	0.99 (0.98-1.01)	0.58
Nephrotoxic co-exposures, n (%)	29 (27.4)	12 (42.9)	17 (21.8)	0.03	1.92 (0.79-4.66)	0.15

Early glycopeptide escalation was defined as initiation of teicoplanin or vancomycin within 48 hours of the onset of febrile neutropenia. Adjusted odds ratios (aORs) were derived from a multivariable logistic regression model with cluster-robust standard errors to account for multiple episodes of febrile neutropenia within the same patient.

*: Adjusted ORs represent independent predictors of early glycopeptide escalation included in the multivariable model; OR: odds ratio; CI: confidence interval; IQR: interquartile range.

Table 3. Acute kidney injury and clinical outcomes by phenotype and early glycopeptide escalation.

Outcome	Overall (n=106)	Phenotype 1 (n=42)	Phenotype 2 (n=24)	Phenotype 3 (n=40)	p	Early escalation (n=28)	No escalation (n=78)	p
Acute kidney injury, n (%)	11 (10.4)	5 (11.9)	5 (20.8)	1 (2.5)	0.03	8 (28.6)	3 (3.8)	<0.001
Peak creatinine ratio, median (IQR)	1.21 (1.05-1.58)	1.34 (1.12-1.72)	1.46 (1.18-1.89)	1.08 (1.02-1.18)	0.002	1.58 (1.22-2.03)	1.12 (1.03-1.29)	<0.001
Day-7 clinical success, n (%)	78 (73.6)	30 (71.4)	16 (66.7)	32 (80.0)	0.42	19 (67.9)	59 (75.6)	0.42
ICU admission, n (%)	9 (8.5)	4 (9.5)	4 (16.7)	1 (2.5)	0.12	5 (17.9)	4 (5.1)	0.04
All-cause mortality at day 30, n (%)	3 (2.8)	1 (2.4)	2 (8.3)	0 (0.0)	0.18	2 (7.1)	1 (1.3)	0.23

The timing of AKI onset relative to glycopeptide exposure could not be determined due to the study's retrospective design. AKI was defined according to the KDIGO creatinine-based criteria. The peak creatinine ratio was defined as peak serum creatinine divided by baseline creatinine. Day-7 clinical success was defined as defervescence and clinical stability without the need for further antimicrobial escalation or intensive care unit admission.

IQR: Interquartile range; ICU: intensive care unit; AKI: acute kidney injury; KDIGO: Kidney Disease: Improving Global Outcomes.

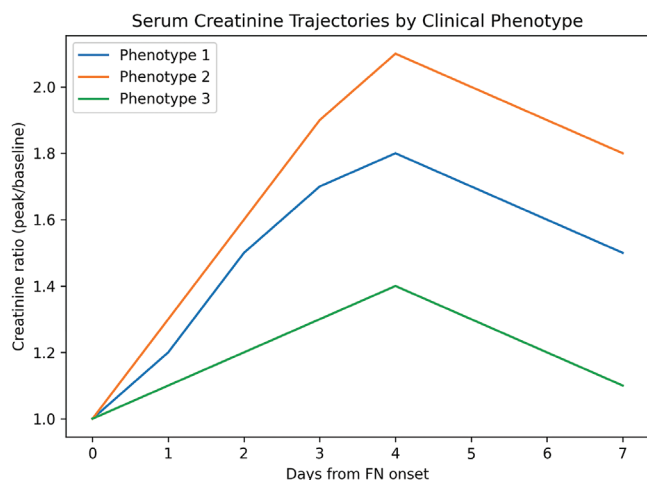


Figure 2. Temporal trajectories of serum creatinine ratios stratified by clinical phenotype. Phenotypes 1 and 2 demonstrate higher and more sustained creatinine elevations compared to the lower-severity phenotype, consistent with the clustering of acute kidney injury within escalation-prone phenotypic subgroups. The observed decline in creatinine after day 4 may reflect clinical recovery and/or treatment modification; however, detailed data on glycopeptide discontinuation or dose adjustment were not systematically available.

FN: Febrile neutropenia.

routine clinical practice in FN and underscores that renal injury clustered within specific clinical phenotypes rather than being solely attributable to documented suprathreshold exposure.

Our findings expand on the literature showing that early glycopeptide escalation does not improve short-term clinical outcomes in unselected pediatric FN populations [7,8,9,13,14,15]. While previous studies and meta-analyses have largely addressed average treatment effects, our phenotype-based approach reveals that escalation behavior is not randomly distributed across FN episodes. Instead, it concentrates within specific clinical contexts marked by non-specific severity cues, including elevated inflammatory burden, severe mucositis, suspected sepsis, typhlitis, and early hemodynamic deterioration. This observation provides a mechanistic explanation for the persistent clinical overuse of glycopeptides despite long-standing guideline recommendations to reserve these agents for narrowly defined indications [4,5,6].

A key novel contribution of this study is the demonstration that renal toxicity signals preferentially cluster within escalation-prone phenotypes. AKI occurred almost exclusively within phenotypes characterized by heightened inflammatory burden and clinical deterioration, accounting for over 90% of AKI events. Both vancomycin and teicoplanin have been previously implicated in nephrotoxicity, particularly in pediatric oncology populations exposed to multiple concurrent nephrotoxic agents [20,21,22,23,24,25,26,27]. However, our findings suggest that glycopeptide-associated renal injury may be synergistically

amplified by host vulnerability and contextual severity rather than representing a uniform drug effect across all FN episodes. In this regard, renal toxicity emerges as a phenotype-contingent safety signal rather than a diffuse population-level risk. Importantly, the temporal relationship between glycopeptide initiation and AKI onset cannot be definitively established in this retrospective analysis. It is possible that early renal injury was already evolving in escalation-prone phenotypes prior to glycopeptide exposure, reflecting underlying clinical severity rather than a direct drug effect alone. This suggests that glycopeptide-associated AKI may represent a context-dependent phenomenon driven by host vulnerability and illness severity, rather than a uniform pharmacological effect across all FN episodes.

Notably, agent selection patterns further illuminate the behavioral dimension of escalation. Vancomycin use was heavily concentrated within the hemodynamically severe phenotype enriched for typhlitis and early shock, whereas teicoplanin predominated within the high-inflammatory/mucositis-dominant phenotype. These patterns likely reflect distinct clinician heuristics, with vancomycin as a reflexive escalation in the context of perceived septic risk and gastrointestinal translocation, and teicoplanin as an escalation in response to inflammatory uncertainty and mucosal barrier injury. Importantly, both escalation pathways were largely decoupled from microbiological confirmation, reinforcing concerns that escalation decisions are frequently driven by evolving clinical concern rather than pathogen-directed evidence [10,11,12,28,29]. This distinction provides a more nuanced understanding of how and why guideline-discordant glycopeptide use persists in daily pediatric FN care.

From a methodological perspective, this study advances a novel analytic paradigm by integrating unsupervised phenotyping with escalation behavior and renal safety outcomes. Similar data-driven frameworks have successfully identified clinically meaningful phenotypes in sepsis and acute respiratory distress syndrome, with implications for both prognostication and therapeutic targeting [22,23,24]. In pediatric FN, however, such approaches remain underutilized. By demonstrating that both escalation behavior and toxicity signals align with latent clinical phenotypes, our findings challenge the prevailing assumption that FN represents a homogeneous risk state and that escalation decisions carry uniform risk-benefit tradeoffs.

Confounding by indication constitutes an inherent challenge in observational analyses of clinician-driven escalation decisions [16,17]. To mitigate the impact of this bias, we applied propensity score-based IPTW and phenotype-stratified sensitivity analyses. Although these approaches strengthened the causal plausibility, residual confounding cannot be fully excluded. In particular, unmeasured severity cues, clinician risk tolerance, and institutional practice patterns may have influenced escalation

behavior and renal outcomes. Nonetheless, the consistent clustering of AKI within escalation-prone phenotypes, even after adjustment, supports the robustness of our central findings.

These results have important implications for antimicrobial stewardship in pediatric FN. First, they support a shift from binary escalation algorithms toward phenotype-informed decision frameworks that explicitly acknowledge clinical heterogeneity and contextual vulnerability. Second, they underscore the need to reconceptualize early glycopeptide escalation not merely as a therapeutic intervention but as a behavioral response to uncertainty that may confer disproportionate toxicity risk in specific phenotypic contexts. Third, they suggest that renal safety monitoring and nephrotoxic risk mitigation strategies should be preferentially targeted toward escalation-prone phenotypes, where harm signals cluster most densely.

Study Limitations

The retrospective single-center design of this study limited its generalizability and the ability to establish causal inference. Although we employed cluster-robust regression, IPTW, and sensitivity analyses to mitigate confounding by indication, residual confounding remained possible. The modest sample size constrained the statistical power for detecting small phenotype-specific differences in rare outcomes. The creatinine-based KDIGO criteria may underestimate subclinical renal injury, and drug exposure metrics such as vancomycin trough concentrations were not systematically available. In addition, the unsupervised clustering approach is inherently sensitive to variable selection and scaling choices. Finally, escalation timing and agent selection reflected local practice patterns and may not be generalizable to other institutions. In addition, detailed data on glycopeptide dose adjustment or discontinuation following creatinine elevation were not systematically available, limiting the interpretation of post-escalation renal trajectories.

Despite these limitations, this study has several strengths. All FN episodes were initially managed with a uniform empiric regimen, minimizing the baseline treatment heterogeneity. Escalation timing and agent selection were prospectively documented in contemporaneous clinical records. Phenotype derivation relied exclusively on baseline variables available at FN onset, enhancing the clinical applicability. To our knowledge, this is the first study to simultaneously evaluate clinical phenotypes, escalation behavior, and renal toxicity clustering within pediatric FN.

Conclusion

Pediatric FN comprises distinct clinical phenotypes that differentially drive early glycopeptide escalation behavior and renal safety signals. Escalation-prone phenotypes exhibit disproportionate clustering of AKI without corresponding short-term clinical benefit. By reframing escalation as a phenotype-

contingent behavioral response rather than a uniform therapeutic act, our findings advance a framework for context-sensitive precision stewardship for antimicrobial decision-making during pediatric FN management. Future multicenter prospective studies are needed to validate these phenotypes, refine escalation thresholds, and clarify temporal relationships and causal pathways between escalation practices and renal outcomes, ultimately determining whether phenotype-guided strategies can improve both safety and value of care.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, İzmir City Hospital Non-Interventional Ethics Committee (decision date: 17.12.2025; decision no: 2025/556).

Informed Consent: The requirement for informed consent was waived due to the retrospective design of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.T., Ş.Ö.A.; Concept: N.T., B.T.G., Ş.Ö.A.; Design: N.T.; Data Collection or Processing: N.T., Z.Ö.S., M.E., B.T.G., Ş.Ö.A.; Analysis or Interpretation: N.T., M.E., E.Ö.; Literature Search: Z.Ö.S.; Writing: N.T., B.T.G., S.G.

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