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Association of Neutropenia With One Year Outcomes in Pediatric Kidney Transplant Recipients: A Retrospective Study

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Abstract

Background:

Neutropenia is a frequent complication following pediatric kidney transplantation, often linked to immunosuppressive and prophylactic therapies. The impact of neutropenia on clinical outcomes, such as bacterial infections and transplant rejection, is not well established. This study assessed its association with clinical outcomes during the first year after transplant.

Methods:

We performed a retrospective analysis of pediatric kidney transplant recipients at a tertiary children's hospital between June 2018 and June 2023. Multivariable regression analyses assessed associations between neutropenia and one-year post-transplant hospitalization, cytomegalovirus (CMV), Epstein–Barr virus (EBV), and BK polyomavirus (BKPyV) viremia, as well for decline in estimated glomerular filtration rate (eGFR). Therapeutic interventions prompted by neutropenia were also described.

Results:

Fifty-three patients were included (median age at transplant 10.8 years; 52.8% male) all of whom completed 1 year of follow-up. Thirty-five (66%) experienced 68 neutropenia episodes within the first year. Neutropenia was not associated with hospitalization for bacterial infections (IRR 1.00, 95% CI 0.58–1.73), CMV (OR 0.85, 95% CI 0.18–3.94), EBV (OR 1.06, 95% CI 0.22–5.10), BKPyV viremia (OR 0.52, 95% CI 0.12–2.23), or eGFR decline (β = 0.2, 95% CI − 5.2 to 32.9). In response to neutropenia, 74 treatment modifications occurred: trimethoprim-sulfamethoxazole was reduced in 25.7%; mycophenolate mofetil (MMF) was reduced in 16.2% and discontinued in 1.4%; valganciclovir was reduced in 8.1% and discontinued in 21.6%.

Conclusion:

Neutropenia after pediatric kidney transplantation was not associated with bacterial infection-related hospitalizations, viremia, acute rejection, or impaired graft function during the first year post-transplant.

Introduction

Kidney transplantation remains the gold standard treatment for pediatric patients with kidney failure, offering a significant survival advantage and improved quality of life compared to dialysis. Over recent decades, both graft and patient survival rates have improved substantially, reflecting advancements in surgical techniques, immunosuppressive therapy, and post-transplant care [1, 2]. Despite these achievements, post-transplant complications continue to pose significant clinical challenges. Among these, hematologic abnormalities, particularly neutropenia, are commonly encountered and require careful management and monitoring [3].

Neutropenia, typically defined as an absolute neutrophil count (ANC) of less than 1.5×10^9/L, is a frequent complication following kidney transplantation, occurring in up to 50% of pediatric recipients within the first post-transplant year [3]. Most cases of neutropenia are acquired, with common etiologies including infections, autoimmune processes, and drug-induced myelosuppression [3, 4].

Persistent and severe neutropenia increases the risk of infectious complications, particularly bacterial infections such as urinary tract infections, as well as viral and opportunistic infections. Conversely, modifying the immunosuppressive regimen, most commonly through dose reduction or temporary discontinuation of agents like mycophenolate mofetil, to manage neutropenia may lead to an increased risk of acute rejection. Transplant physicians commonly face the challenge of balancing the risk of cytopenia, particularly neutropenia, against the risk of rejection, which requires thoughtful modification of the immunosuppressive regimen [5–8].

Despite the high frequency of neutropenia after kidney transplantation, evidence regarding its clinical impact remains limited, particularly in pediatric recipients. Few studies have provided descriptive data on cytopenias in solid organ transplant recipients [9], while others have examined the association between neutropenia and allograft rejection [10]. However, comprehensive evaluations of clinically relevant outcomes, including infections, hospitalization, and graft function, are lacking. Further studies, particularly in pediatric kidney transplant recipients, are needed to clarify the clinical significance of neutropenia and support clinical decision-making.

To address these gaps in understanding, this study investigates the relationship between post-transplant neutropenia and clinical outcomes during the first year after kidney transplantation in a pediatric population.

Methods

Study Population

This retrospective cohort study was conducted at a single tertiary center and included all pediatric patients under the age of 18 years who underwent kidney transplantation at The Hospital for Sick Children between June, 2018, and June, 2022. Patients with at least one year of post-transplant follow-up were included. Patients with underlying conditions known to predispose to neutropenia, including prior hematopoietic stem cell transplantation, chemotherapy, multiorgan transplantation, or a documented diagnosis of chronic neutropenia, were excluded from the analysis.

Ethics approval for this study was obtained from the Research Ethics Board at The Hospital for Sick Children (REB # 1000081403).

Data collection

Demographic, clinical, and laboratory data were extracted from the institutional electronic health records. Collected data included age at transplant, sex, and pre-transplant CMV and EBV status. Details of induction and maintenance immunosuppressive therapy were also recorded. Absolute neutrophil count (ANC) and creatinine level were documented, along with relevant outcomes captured during both inpatient and outpatient encounters within the first-year post-transplant. These outcomes included the total number of hospitalizations for each patient, with specific documentation of admissions attributed to bacterial infections, as well as biopsy-confirmed acute rejection events, episodes of viremia, and any adjustments to or discontinuation of immunosuppressive and anti-infectives medications in response to neutropenia.

Study Definitions

Neutropenia events: Neutropenia was defined as two consecutive ANC measurements ≤ 1500/μL, measured at least 24 hours apart. Severity was categorized based on the nadir ANC value as follows: mild (1000 − 1500/μL), moderate (500–999/μL), and severe (< 500/μL). In patients with multiple neutropenia episodes, each was counted separately if resolution was documented. Resolution was defined as an ANC > 1500/μL on two consecutive measurements at least 24 hours apart.

Hospitalizations due to bacterial infection: Hospital admissions were considered attributable to bacterial infection when the treating physician presumed a bacterial etiology based on clinical assessment and initiated a full course of antibiotic therapy.

Viremia: Viremia was defined as CMV, EBV, or BKPyV viral load ≥ 1000 copies/mL.

Acute Rejection: Rejection episodes included biopsy proven cases of antibody-mediated rejection (ABMR) or T cell-mediated rejection (TCMR), as defined by the Banff 2017 revised criteria.

eGFR decline: The difference between eGFR at 1-year post-transplant and eGFR at discharge from the transplant admission.

Immunosuppression and anti-infectives medications

Immunosuppression medications were tailored according to immunological risk. Low-risk recipients received basiliximab induction, whereas high-risk recipients received anti-thymocyte globulin (rabbit) induction. All patients received maintenance therapy with tacrolimus, mycophenolate mofetil, initial dose 600 mg/m²/day, titrated to 1200 mg/m²/day as tolerated, and corticosteroids according to a standardized institutional protocol with gradual corticosteroid tapering. Tacrolimus target trough concentrations were 10–12 ng/mL during the first 3 months, 7–9 ng/mL during months 4–6, and 4–6 ng/mL through the end of the first post-transplant year.

Antiviral prophylaxis was based on donor/recipient CMV and EBV serostatus and consisted of ganciclovir, valganciclovir, or acyclovir according to individual risk stratification. Trimethoprim-sulfamethoxazole was administered for Pneumocystis jirovecii pneumonia and urinary tract infection prophylaxis during the first 6 months after transplantation.

Statistical analysis

Continuous variables were presented as means and standard deviation (SD) for normally distributed data, and as medians with interquartile ranges (IQR) for non-normally distributed data. Categorical variables were presented as frequencies and percentages. Univariate analyses were performed to compare baseline characteristics and clinical outcomes between patients with and without neutropenia. Categorical variables were analyzed using the chi-square test, whereas continuous variables were compared using the independent samples t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables.

Logistic regression analysis was used to evaluate the association between neutropenia and EBV, CMV, and BKPyV viremia. Poisson regression analysis was applied to assess count outcomes, including the number of hospitalizations. Linear regression analysis was performed to examine the association between neutropenia and eGFR decline.

All analyses were performed using SPSS statistics software, version 29.0. with a statistical significance considered as P value < 0.05.

Results

Patient Characteristics

A total of 53 pediatric kidney transplant recipients were included. Median age at transplant was 10.8 years (IQR 5.2–14.9); 52.8% were male. A higher proportion of patients in the neutropenic group were at high EBV risk (60% vs. 27.8%), other baseline characteristics were comparable between the neutropenic and non-neutropenic groups (Table 1). Basiliximab was the most used induction agent in both groups. All patients received standard triple maintenance immunosuppression with prednisolone, mycophenolate mofetil and tacrolimus.

Table 1
Baseline demographic and clinical characteristics of pediatric kidney transplant recipients by the development of post-transplant neutropenia.

Characteristics		**Neutropenia (n = 35)**	**No neutropenia (n = 18)**
Recipient age (y), median (IQR)		10.1(4.5–14.2)	11.3 (6.4–14.9)
Male Sex, n (%)		18 (51.4)	10 (55.6)
Induction therapy, n (%)	Basiliximab	30 (85.7)	14 (77.8)
	Anti-thymocyte Globulin (rabbit)	5 (14.3)	4 (22.2)
CMV risk[a], n (%)	High	8 (22.9)	3 (16.7)
	Moderate	13 (37.1)	7(38.9)
	Low	14 (40)	8 (44.4)
EBV risk[a], n (%)	High	21 (60)	5 (27.8)
	Moderate	10 (28.6)	5 (27.8)
	Low	4 (11.4)	8 (44.4)
Time to neutropenia (d), median (IQR)		77 (60–118)	
Neutropenia severity, n (%)	Mild	10 (28.6%)	
	Moderate	18 (51.4%)	
	Severe	7 (20%)	

[a] High risk serostatus – recipient negative, donor positive; Moderate risk– recipient positive, donor positive or negative; Low risk serostatus – recipient negative, donor negative

Thirty-five patients (66%) developed at least one episode of neutropenia during the first post-transplant year, a total of 68 neutropenia events were recorded. The median time to the first neutropenia episode was 77 days (IQR, 60–118). Among neutropenic patients, 28.6% had mild neutropenia, 51.4% moderate, and 20% severe.

Clinical Outcomes

A total of 168 hospitalizations occurred within one year post transplantation. The median number of hospitalizations per patient was 2 [IQR 1–5] in the neutropenia group compared with 2.5 [IQR 1–4] in the non-neutropenia group. In multivariable analysis, there was no significant difference in hospitalization rate between the two groups (IRR = 1.00, 95% CI 0.7–1.4, p = 1.0).

A total of 63 hospitalizations were attributed to bacterial infections. The median number of infection related hospitalizations per patient was higher in the neutropenic group. However, in multivariable analysis, there was no significant difference between the groups (IRR = 1.00, 95% CI 0.6–1.7, p = 1.0).

CMV viremia occurred at similar rates in the neutropenia and non-neutropenia groups. EBV viremia was more frequent among patients with neutropenia, whereas BKPyV viremia was more common among those without neutropenia. In multivariable analysis, neutropenia was not significantly associated with CMV (OR 0.9, 95% CI 0.2–3.9, p = 0.8), EBV (OR 1.1, 95% CI 0.2–5.1, p = 0.9), or BKPyV viremia (OR 0.5, 95% CI 0.1–2.2, p = 0.4).

There were seven documented episodes of acute rejection, 4 (11.4%) in the neutropenia group and 3 (16.7%) in the non-neutropenia group. Univariate analysis showed no statistically significant association between neutropenia and acute rejection (OR = 0.7, 95% CI 0.13–3.3, p = 0.6). The number of events was insufficient to perform multivariable analysis.

Both groups experienced a decline in eGFR within the first-year post-transplant. The median decline was 25 mL/min/1.73m² (IQR 9.3–63.9) in the neutropenia group compared with 16.6 mL/min/1.73m² (IQR 9.7–30.1) in the non-neutropenia group. In multivariable analysis, this difference was not statistically significant (β = 0.2, 95% CI − 5.2 to 32.9, p = 0.2) (Tables 2 and 3).

Table 2
Clinical outcomes during the first year after transplantation in pediatric kidney transplant recipients with and without post-transplant neutropenia

Outcome	**Neutropenia (n = 35)**	**No neutropenia (n = 18)**
Total hospitalization, median (IQR)	2 (1–5)	2.5 (1–4)
Infection related hospitalizations, median (IQR)	1 (0–1)	0 (0–2)
CMV viremia, n (%)	8 (22.9)	4 (22.2)
EBV viremia, n (%)	14 (40)	4 (22.2)
BKPyV viremia, n (%)	6 (17.1)	5 (27.8)
Rejection, n (%)	4 (11.4)	3 (16.7)
eGFR decline, median (IQR)	25 (9.3–63.9)	16.6 (9.7–30.1)

Table 3
Multivariable analysis of the association between post-transplant neutropenia and 1-year clinical outcomes in pediatric kidney transplant recipients

Outcome	Effect estimate (95% CI)	P-value	Effect estimate (95% CI)	P-value
Total hospitalization[s]	0.9 (0.7–1.3)	0.6	1.00 (0.7–1.4)	1.0
Infection related hospitalizations[b]	1.0 (0.6–1.6)	0.9	1 (0.6–1.7)	1.0
CMV viremia[c]	1.0 (0.3–4.1)	1.0	0.9 (0.2–3.9)	0.8
EBV viremia[d]	2.3 (0.6–8.6)	0.2	1.1 (0.2–5.1)	0.9
BKPyV viremia[e]	0.5 (0.1–2.1)	0.4	0.5 (0.1–2.2)	0.4
eGFR decline[f]	0.2 (-4.2-34.9)	0.1	0.2 (-5.2–32.9)	0.2
[a] Poisson regression adjusted for age at transplant.				
[b] Poisson regression adjusted for age at transplant, sex and CMV risk.				
[c] Logistic regression adjusted for CMV risk.				
[d] Logistic regression adjusted for age at transplant and EBV risk.				
[e] Logistic regression adjusted for sex and CMV risk.				
[f] Linear regression adjusted for age at transplant and sex.				

Therapeutic Interventions

A total of 74 medication adjustments were documented in response to neutropenia. The most frequently modified medications were trimethoprim-sulfamethoxazole and valganciclovir. Trimethoprim-sulfamethoxazole was reduced in 19 events (25.7%) and discontinued in 15 (20.2%). Valganciclovir was reduced in 6 instances (8.1%) and stopped in 16 (21.6%). MMF was reduced in 12 events (16.2%) and stopped in 1 event (1.4%). G-CSF was administered in 5 patients (Table 4).

Table 4
Medication modifications and G-CSF use in response to post-transplant neutropenia during the first year after kidney transplantation

Medication modifications	**Intervention[a] (n = 74)**
MMF reduced	12 (16.2)
MMF stopped	1 (1.4)
Trimethoprim-sulfamethoxazole reduced	19 (25.7)
Trimethoprim-sulfamethoxazole stopped	15 (20.2)
Valganciclovir reduced	6 (8.1)
Valganciclovir stopped	16 (21.6)
Ganciclovir reduced	0
Ganciclovir stopped	0
G-CSF use	5 (6.8)

[a] number of interventions and % from the total intervention

Discussion

In this single-center retrospective cohort study, we investigated the clinical implications of neutropenia in pediatric kidney transplant recipients during the first-year post-transplantation. Our findings suggest that although neutropenia is a common occurrence, affecting approximately two-thirds of the cohort; it was not associated with adverse clinical outcomes, including admission due to bacterial infections, viremia, acute rejection, or impact on graft function.

The overall incidence of neutropenia observed in our cohort is consistent with prior pediatric studies, which have reported rates ranging from 30–70% depending on the definitions used [10–13]. Importantly, the majority of neutropenia episodes in our study were of mild to moderate severity, and only a minority (20%) reached an ANC < 500/μL and deemed most severe. Although prior studies have reported an increased infectious risk associated with neutropenia [10, 14] we found no statistically significant difference in hospitalization rates for bacterial infections between patients with and without neutropenia. Moreover, no statistically significant differences in viremia were observed between neutropenic and non-neutropenic patients. Our findings align with previous adult studies suggesting that the presence of neutropenia may not increase the risk for infections, especially if the neutropenia is mild [5, 15].

We showed in our study there was a high rate of medication adjustment in response to neutropenia, most often dose modification or discontinuation of prophylactic anti-infectives or immunosuppressive medications. Trimethoprim-sulfamethoxazole and valganciclovir, both known myelosuppressive agents,

were the most commonly adjusted, with MMF modification occurring less frequently. The relatively conservative approach to MMF reduction in our cohort may partially explain the absence of a significant increase in acute rejection events. This is an important consideration, as prior reports have linked MMF withdrawal to heightened rejection risk [10, 11]. Additionally, both study groups experienced a decline in eGFR within the first year after transplantation, however, this difference was not statistically significant. Similar results have been reported in previous studies, which also found no difference in graft survival at 10 years post-transplant (5).

Despite frequent medication adjustments, the lack of adverse outcomes raises an important question: should all episodes of neutropenia in pediatric kidney transplant patients prompt intervention? Current clinical guidelines offer limited direction, and treatment decisions are often based on perceived rather than demonstrated risk. Within this cohort, few patients underwent reduction in immunosuppression, and no increased risk of infection was observed, which may support a cautious approach to medication adjustment in selected patients. This reinforces the value of an individualized approach to managing neutropenia, especially when episodes are mild, transient, and not accompanied by clinical complications.

Our study has several limitations that should be considered when interpreting the findings. First, the relatively small sample size may have limited our ability to detect significant associations, particularly for infrequent but clinically meaningful outcomes such as viremia or rejection. However, we had complete one year data on all participants and hospitalization happen primarily at the tertiary center preventing missing data. Second, the retrospective design limits our ability to determine causal relationships between neutropenia and bacterial hospitalizations, as well as between medication adjustments made in response to neutropenia and subsequent viremia or rejection. Additionally, graft function was evaluated only within the first-year post-transplant, and we lacked long-term follow-up data to assess potential delayed effects of neutropenia on kidney function.

Despite these limitations, our study offers several notable strengths. It focuses exclusively on a pediatric kidney transplant population, an area with limited existing data, and includes detailed characterization of neutropenia, including its severity, timing, and the therapeutic interventions it prompted. Additionally, the comprehensive collection of clinical outcome data within the first-year post-transplant allowed for a thorough assessment of the potential impact of neutropenia on important clinical endpoints.

Conclusion

Neutropenia is a common complication after pediatric kidney transplantation; however, in this study, it was not associated with worse short-term clinical outcomes such as infection, rejection, or decline in graft function. In this cohort, the careful and limited use of MMF reduction in response to neutropenia appeared to be safe, supporting an individualized approach to management.

Declarations

The authors have no relevant financial or non-financial interests to disclose. The authors did not receive support from any organization for the submitted work.

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