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Outcomes of granulocyte colony-stimulating factor use in pediatric kidney transplant recipients: A Pediatric Nephrology Research Consortium study

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Abstract

Background: Neutropenia is common in the first year after pediatric kidney transplant and is associated with an increased risk of infection, allograft loss, and death. Granulocyte colony-stimulating factor (G-CSF) increases neutrophil production, but its use in pediatric solid organ transplant recipients remains largely undescribed.

Methods: We performed a multicenter retrospective cohort study of children with neutropenia within the first 180 days after kidney transplant. Multivariable linear regression and Poisson regression were used to assess duration of neutropenia and incidence of hospitalization, infection, and rejection.

Results: Of 341 neutropenic patients, 83 received G-CSF during their first episode of neutropenia. Median dose of G-CSF was 5 mcg/kg for 3 (IQR 2–7) doses. G-CSF use was associated with transplant center, induction immunosuppression, steroid-free maintenance immunosuppression, hospitalization, and decreases in mycophenolate mofetil, valganciclovir, and trimethoprim–sulfamethoxazole dosing. Absolute

Abbreviations: aIRR, adjusted incidence rate ratio; ANC, absolute neutrophil count; CAKUT, congenital anomalies of the kidney and urinary tract; CMV, cytomegalovirus; D-, donor immunoglobulin G negative; D+, donor immunoglobulin G positive; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; G-CSF, granulocyte colony-stimulating factor; IQR, interquartile range; MMF, mycophenolate mofetil; OR, odds ratio; PTLD, post-transplant lymphoproliferative disease; R-, recipient immunoglobulin G negative; R+, recipient immunoglobulin positive; TMP-SMX, trimethoprim–sulfamethoxazole.

neutrophil count nadir was also significantly lower among those treated with G-CSF. G-CSF use was not associated with a shorter duration of neutropenia ($p = .313$) and was associated with a higher rate of neutropenia relapse ($p = .002$) in adjusted analysis. G-CSF use was associated with a decreased risk of hospitalization (aIRR 0.25 (95%CI 0.12–0.53) $p < .001$) but there was no association with incidence of bacterial infection or rejection within 90 days of neutropenic episode.

Conclusion: G-CSF use for neutropenia in pediatric kidney transplant recipients did not shorten the overall duration of neutropenia but was associated with lower risk of hospitalization. Prospective studies are needed to determine which patients may benefit from G-CSF treatment.

KEYWORDS
adverse effect, neutropenia, pediatric, pediatric kidney transplant, G-CSF

1 | BACKGROUND

Immunosuppressive medications and infection prophylaxis are the bedrock underlying modern success in solid organ transplantation, but neutropenia is a common and concerning side-effect for many essential medications. Neutropenia affects approximately 64% of pediatric kidney transplant recipients in the first year after transplant[1] and is associated with increased risk of bacterial infection,[2] allograft loss, and death.[3] Mycophenolate mofetil and valganciclovir are the medications most commonly associated with neutropenia, although tacrolimus, sirolimus, thymoglobulin, trimethoprim–sulfamethoxazole, and omeprazole also pose a risk.[2] Decreasing or stopping mycophenolate mofetil is a common treatment for post-transplant neutropenia, but is associated with an increased risk of rejection, with a hazard ratio of 1.11 per day off medication.[2]

Granulocyte colony-stimulating factor (G-CSF) is well-studied in the oncology literature as a means to increase neutrophil production and shorten the duration of neutropenia.[4] Its use in the solid organ transplant population is less well-established. A study by Turgeon et al. showed that G-CSF use in liver and kidney graft recipients with neutropenia could successfully increase the white blood cell count, but reported an 8% incidence of rejection within 2 months of using the drug.[5] On the other hand, a review of Medicare claims by Hurst et al. showed no increased risk of allograft loss among 740 kidney transplant patients treated with G-CSF.[3]

In this study, we sought to assess whether or not G-CSF is effective at decreasing the duration of neutropenia and incidence of hospitalization among pediatric kidney transplant recipients and to assess whether or not G-CSF use is associated with an increased risk of acute rejection or neutropenia relapse in this population.

2 | METHODS

We performed a multicenter retrospective cohort study among centers participating in the Pediatric Nephrology Research Consortium, a group of 73 pediatric nephrology centers that collaborate to perform research in pediatric nephrology. Thirteen pediatric transplant centers elected to participate and contribute patients. Patients 17 years of age or less who received a kidney transplant between January 1, 2008 and December 31, 2017 and subsequently developed an absolute neutrophil count (ANC) less than 1500/mm^3 within 180 days after transplantation were included in the study. Patients were excluded if they had a pre-existing diagnosis of neutropenia, such as congenital neutropenia or cyclic neutropenia, a history of hematopoietic stem cell transplantation or other non-renal solid organ transplant, a diagnosis of post-transplant lymphoproliferative disorder (PTLD) prior to the development of neutropenia, received chemotherapy for any malignancy within the first year post-transplant, or had less than 1 year of follow-up. Patients were then divided into those who did and did not receive treatment with granulocyte colony-stimulating factor (G-CSF) during their first neutropenic episode for further analysis.

The primary outcome of interest was duration of neutropenia. Onset of neutropenia was defined as the first day on which the ANC was less than 1500/mm^3 for at least two consecutive measurements at least 24 h apart; resolution of neutropenia was defined as the first day on which the ANC was 1500/mm^3 or higher for at least two consecutive measurements at least 24 h apart. Data were collected on potential confounders of neutropenia duration, including transplant center, adjustment of other immunosuppression or potential neutropenia-inducing medications, nadir ANC, concomitant infections, induction immunosuppression, steroid maintenance immunosuppression, and duration of neutropenia prior to G-CSF initiation.

The most common G-CSF side-effects are fever, bone pain, nausea, and thrombocytopenia, which are well-documented. Given concern that these side-effects may not be well-recorded in the medical record of all participating centers, we elected to focus data collection on potential transplant-specific side-effects, including estimated glomerular filtration rate (eGFR) at one year post-transplant and incidence rates of acute rejection and PTLD. Other secondary outcomes included the incidence of neutropenia relapse and incidence rates

of hospitalization and bacterial infection. Neutropenia relapse was defined as an ANC <1500/mm^3 on two consecutive measurements at least 24 h apart after resolution of the first neutropenia episode within 180-days post-transplant. Acute rejection was defined as biopsy-proven acute cellular or antibody-mediated rejection during the episode of neutropenia or within 90 days of its resolution, as assessed by local center pathologists. Bacterial infection was defined as a clinical diagnosis of infection by treating physicians and either a positive culture result or treatment with antibiotics. eGFR at one-year post-transplant was calculated using the bedside Schwartz equation.[6]

Data were collected from the medical record by individual transplant centers and submitted to the study via a REDCap database. The study was powered for the rarest outcome, biopsy-proven acute rejection, with an estimated sample size of 215 patients (43 treated with G-CSF and 172 neutropenic controls) to provide 80% power to detect a relative risk of rejection of 2.5 with a type 1 error rate of 5%. Data analysis was performed using STATA/SE 15.1. Descriptive statistics used means for normally distributed data and medians for skewed data. Univariable differences between those who were and were not treated with G-CSF were compared using *t*-tests, Chi-squared test, and Fisher exact tests, as appropriate. Duration of neutropenia and neutropenia relapse were assessed using multivariable linear regression for continuous outcomes and multivariable logistic regression for dichotomous outcomes, with adjustment for transplant center, nadir ANC, induction immunosuppression, and dosing of mycophenolate mofetil, valganciclovir, and trimethoprim–sulfamethoxazole. Incidence of hospitalization, infection, rejection, and PTLD were reported as incidence rates, with patients contributing person-time to the 'No G-CSF' group until 3 days after the first dose of G-CSF (to allow time for the medication to take effect). Adjusted incidence rate ratios were calculated using Poisson regression, accounting for the same confounding variables.

This study was approved by each center's local Institutional Review Board.

3 | RESULTS

3.1 | Demographics

This study enrolled 341 neutropenic pediatric kidney transplant recipients from 13 transplant centers, of whom 94 (27.6%) were treated with at least one course of G-CSF (Table 1). Median time to onset of neutropenia was 81 days (IQR 44–103 days) post-transplant and did not differ between groups. Eighty-three patients received G-CSF during their first episode of neutropenia and were included in the primary analysis, while 11 were treated for a recurrent episode of neutropenia. Median time from onset of neutropenia to initiation of G-CSF was 7 days (IQR 2–16 days). G-CSF was dosed at a median of 5 mcg/kg for three doses (IQR 2–7 doses), and neutropenia resolved at a median of 11 days (IQR 5–34 days) after G-CSF initiation.

Among the 13 participating transplant centers enrolling patients, 11 centers prescribed G-CSF to at least a portion of their neutropenic transplant recipients, but only four centers prescribed G-CSF in more than 40% of cases. Two centers did not prescribe G-CSF to any patient. Ten of 13 centers, comprising 78% of the study population, used IL-2 blockade for induction immunosuppression in at least a portion of their patients. Seven centers, comprising 66.6% of the study population, used thymoglobulin as the alternative induction agent while five centers, comprising 32.6% of the study population used alemtuzumab as an alternative. There was no association between transplant center and ANC nadir. ANC nadir was lower among patient receiving alemtuzumab immunosuppression compared to thymoglobulin or IL-2 blockade.

3.2 | Factors associated with G-CSF treatment

Univariable analysis showed a statistical association between G-CSF use and transplant center. There was also a positive correlation between G-CSF treatment and induction immunosuppression (alemtuzumab or thymoglobulin compared to IL-2 blockade), hospitalization, and decreases in mycophenolate mofetil, valganciclovir, and trimethoprim sulfamethoxazole dosing. G-CSF treatment was negatively correlated with steroid-free immunosuppression and ANC nadir. Specifically, G-CSF was given to 51.4% of patients with an ANC <500/mm^3 compared to 11.3% of those with an ANC ≥500/mm^3, an association that remained significant even after adjusting for transplant center ($p < .001$). No patient with an ANC nadir greater than 1000/mm^3 was treated with G-CSF. Similarly, G-CSF was given to 40.9% of patients who were hospitalized while neutropenic compared to 18.2% of those who were not hospitalized ($p = .03$ after adjusting for transplant center and ANC nadir). There was no association between G-CSF treatment and patient age, CMV viremia, or EBV viremia (Table 2).

3.3 | Duration of neutropenia

There was no difference in duration of the first episode of neutropenia between those who were (median 21 days (IQR 10–49 days) and were not (median 21 days (IQR 10–42 days) treated with G-CSF in an adjusted analysis ($p = .313$). Neutropenia relapse occurred in 32.3% of the study population; however, the odds of relapse were 4.6 times higher (95%CI 1.8–12.0) in patients treated with G-CSF ($p = .002$) when adjusting for transplant center, nadir ANC, induction immunosuppression, and adjustments to trimethoprim–sulfamethoxazole, valganciclovir, and mycophenolate mofetil doses. Median time to relapse (21 days (IQR 14–42 days), and median duration of relapse (28 days (IQR 14–50 days)) did not differ between groups. Nadir ANC with relapse was lower in the G-CSF-treated group (461/mm^3 (IQR 270–800/mm^3) than in the untreated group (753/mm^3 (IQR 476–1149/mm^3), but this difference was not statistically significant after adjusting for transplant center and induction immunosuppression.

TABLE 1 Demographics of pediatric kidney transplant recipients with neutropenia within the first 180 days post-transplant at 13 Pediatric Nephrology Research Consortium centers, 1/1/2008-12/31/2017

	G-CSF ($n = 83$)		No G-CSF ($n = 258$)		
	n or median	(IQR) or (%)	*n* or median	(IQR) or (%)	*p*
Age at transplant (years)	10.8	(4.5–14.1)	11	(4.3–15)	0.719
Male	53	63.9%	167	64.7%	0.885
Race					0.798
Caucasian	61	73.5%	191	74.0%	
African American	10	12.1%	40	15.5%	
Asian	3	3.6%	7	2.7%	
Other/Unknown	9	10.8%	20	8.7%	
Hispanic	15	18.1%	69	26.7%	0.129
Cause of kidney disease					0.079
CAKUT	38	45.8%	128	49.6%	
Nephrotic Syndrome	22	26.5%	32	12.4%	
Glomerulonephritis	4	4.8%	30	11.6%	
Ciliopathy	4	4.8%	23	8.9%	
Other/Unknown	15	18.1%	45	17.7%	
Donor source					0.757
Deceased donor	47	56.6%	134	51.9%	
Living Related	28	33.7%	96	37.2%	
Living Unrelated	8	9.6%	28	10.9%	
CMV IgG					0.602
Donor-/Recipient-	26	31.3%	76	29.6%	
Donor-/Recipient+	6	7.2%	28	10.9%	
Donor+/Recipient+	18	21.7%	55	21.4%	
Donor+/Recipient-	30	36.1%	94	36.6%	
Unknown	3	3.6%	4	15.5%	
EBV IgG					0.177
Donor-/Recipient-	6	7.2%	27	10.5%	
Donor-/Recipient+	2	2.4%	16	6.2%	
Donor+/Recipient+	27	32.5%	87	33.7%	
Donor+/Recipient-	42	50.6%	105	40.7%	
Unknown	6	7.2%	23	8.9%	
Induction					<0.001
Interleukin−2 blockade	28	36.4%	107	42.3%	
Thymoglobulin	12	15.6%	112	44.3%	
Alemtuzumab	37	48.1%	30	11.9%	
Other/Unknown	6	7.2%	9	3.5%	
Delayed Graft Function	1	1.2%	8	3.1%	0.313
Median eGFR prior to neutropenia (ml/min/1.73m2)	85.4	(66.4–112.7)	76.8	(58.7–102.2)	0.659

Abbreviations: CAKUT, congenital anomaly of the kidney and urinary tract; CMV, cytomegalovirus; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; G-CSF, granulocyte colony-stimulating factor.

In an adjusted analysis combining the first and second episodes of neutropenia, treatment with G-CSF was not associated with a difference in the total duration of neutropenia in those treated with G-CSF ($p = .694$). In a sensitivity analysis that removed pre-G-CSF treatment days from the total duration of neutropenia, median total duration of neutropenia was 30 days (IQR 8–60 days) in those treated with G-CSF compared to 32.5 days (IQR 14–63 days) in the untreated group ($p = .081$) (Table 3).

TABLE 2 Characteristics of first neutropenia episode among pediatric kidney transplant recipients at 13 Pediatric Nephrology Research Consortium centers, January 1, 2008 to December 31, 2017

	G-CSF ($n = 83$)		No G-CSF ($n = 258$)		
	n or median	(%) or (IQR)	*n* or median	(%) or (IQR)	*p*
Neutropenia onset (days post-transplant)	72	(42–97)	81.5	(45–105)	0.287
eGFR at onset of neutropenia (ml/min/1.73m^2)	86.2	(66.4–114.1)	77.1	(58.8–105.9)	0.482
eGFR at 1-year post-transplant (ml/min/1.73m^2)	78.2	(63.0–100.4)	77.1	(61.7–94.2)	0.927
Immunosuppression					0.522
Tacrolimus/MMF	76	91.6%	235	91.1%	
Tacrolimus/Azathioprine	2	2.4%	6	2.3%	
Tacrolimus alone	1	1.2%	7	2.7%	
Other	4	4.8%	10	3.9%	
Tacrolimus trough level (ng/ml)	7.8	(7–9)	8	(6.6–10.2)	0.085
Prednisone	24	28.9%	130	50.4%	0.001
Valganciclovir	70	84.3%	235	91.1%	0.082
Trimethoprim/sulfamethoxazole	71	84.5%	221	85.7%	0.979
Concurrent CMV viremia	4	4.8%	13	5.0%	1.000
Concurrent EBV viremia	8	9.6%	26	10.0%	1.000
Nadir ANC (/mm^3)	310	(180–527)	895	(561–1100)	<0.001
MMF or azathioprine changed					<0.001
Decreased	28	34.6%	58	23.3%	
Stopped	24	29.6%	28	11.2%	
Tacrolimus dose changed					0.332
Decreased	2	2.5%	7	2.8%	
Stopped	1	1.3%	0	0%	
Valganciclovir dose changed					<0.001
Decreased	18	26.5%	20	8.5%	
Stopped	19	27.9%	43	18.3%	
TMP-SMX dose changed					<0.001
Decreased	18	25.7%	5	2.3%	
Stopped	11	15.7%	32	14.5%	
Days from neutropenia onset to G-CSF initiation	7	(2–16)			
G-CSF dose (mcg/kg)	5	(5–6.4)			
Number of G-CSF doses	3	(2–7)			
Days of neutropenia after G-CSF	11	(5–34)			

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; G-CSF, granulocyte colony-stimulating factor; MMF, mycophenolate mofetil; TMP-SMX, trimethoprim–sulfamethoxazole.

In a subgroup analysis, 111 patients had ANC nadir <500/mm^3, and 51.4% of those were treated with G-CSF. Median duration of neutropenia was 20 days (IQR 10–42 days) in the G-CSF treated group compared to 44 days (IQR 25–73 days) in the untreated patients. This difference was not statistically significant in an unadjusted ($p = .0917$) or adjusted ($p = .458$) analysis. Median G-CSF dose was 5 mcg/kg for four doses (IQR 2–7 doses). Median days from initiation of G-CSF initiation to resolution of neutropenia was 11 days (IQR 5–34 days). Among those with an ANC <500/mm^3 who were treated with G-CSF, 26.3% of patients had relapse of their neutropenia compared to 24.1% of those who were untreated. Duration of the first and second episodes of neutropenia combined was 38 days (IQR 14–73 days) in the treated group compared to 55 days (IQR 35–84 days) in the untreated group; this was not statistically significant in an unadjusted ($p = .533$) or adjusted ($p = .338$) analysis.

TABLE 3 Duration of neutropenia among pediatric kidney transplant with neutropenia at 13 Pediatric Nephrology Research Consortium centers, January 1, 2008 to December 31, 2017, by treatment with G-CSF

	G-CSF ($n = 83$)		No G-CSF ($n = 258$)		
	n	% or (IQR)	*n*	% or (IQR)	*p**
Duration of neutropenia (days)	21	(10–49)	21	(10–43)	0.313
Neutropenia relapse	29	34.9%	81	31.4%	0.002
Time to relapse (days)	17.5	(7–37)	28	(14–43)	0.272
Time from G-CSF initiation to relapse (days)	21	(5–42)			
Duration of second neutropenia episode (days)	35	(18–64)	24	(14–42)	0.580
ANC nadir with second neutropenia episode (/ mm^3)	461	(270–800)	768	(476–1149)	0.014
Total duration of neutropenia (days)	42	(18–76)	33	(14–63)	0.694

*p values for duration of neutropenia and total duration of neutropenia are adjusted for transplant center, induction immunosuppression, nadir absolute neutrophil count, and changes to mycophenolate mofetil, trimethoprim–sulfamethoxazole, and valganciclovir dosing. G-CSF granulocyte colony-stimulating factor.

TABLE 4 Incidence rate of hospitalization, bacterial infection, rejection, and post-transplant lymphoproliferative disease among pediatric kidney transplant recipients with neutropenia at 13 Pediatric Nephrology Research Consortium centers, January 1, 2008 to December 31, 2017, by treatment with G-CSF

	G-CSF ($n = 83$)	No G-CSF ($n = 258$)			
	Unadjusted IR per 10 000 person-days	Unadjusted IR per 10 000 person-days	aIRR	95%CI	*p*
Hospitalization	31.5	98.2	0.25	0.12–0.53	<0.001
Bacterial Infections	9.4	28.7	0.43	0.11–1.7	0.226
Rejection	9.4	8.3	0.73	0.15–3.7	0.706
PTLD	6.3	5.6	2.9	0.51–16.6	0.231

Note: Incident rate ratios are adjusted for transplant center, induction immunosuppression, nadir absolute neutrophil count, and changes to mycophenolate mofetil, trimethoprim–sulfamethoxazole, and valganciclovir dosing.

Abbreviations: aIRR, adjusted incident rate ratio; G-CSF, granulocyte colony-stimulating factor; IR, incidence rate; PTLD, post-transplant lymphoproliferative disease.

3.4 | Clinical outcomes

Patients treated with G-CSF had a lower unadjusted incidence rate of hospitalization (31.5 per 10000 person-days) compared to those who were not treated with G-CSF (98.2 per 10000 person-days) (adjusted IRR 0.25 (95%CI 0.12–0.53) $p = <.001$). Overall, 17.2% of hospitalizations occurred within 7 days of diagnosis with a bacterial infection; the etiology of other hospitalizations is not known. In a sensitivity analysis excluding those patients who were hospitalized prior to treatment with G-CSF, G-CSF-use was associated with a lower unadjusted incidence rate of hospitalization (30.6 per 10000 compared to 98.2 per 10000), a difference that was statistically significant even after adjustment for confounding variables ($p = .032$). The incidence of rejection during or within 90 days of a neutropenic episode was 2.9%; there was no difference in the adjusted incidence rate of rejection, bacterial infection, or PTLD within one year post-transplant between the two groups. eGFRs were similar between the two groups prior to, at the onset of, and at resolution of neutropenia as well as at one year post-transplant (Table 4).

4 | DISCUSSION

In this large, multicenter, retrospective cohort study of pediatric kidney transplant recipients, we found a similar duration of neutropenia in the G-CSF treated and untreated group. G-CSF was not associated with allograft rejection, PTLD, or changes in eGFR at 1 year post-transplant. There was a lower incidence rate of hospitalization among those who were treated with G-CSF, but this finding should be interpreted cautiously given the lack of information as to why these patients were hospitalized. To our knowledge, this is the largest study of G-CSF use in a pediatric solid organ transplant population.

Randomized controlled trials of G-CSF use in oncology patients have shown a reduction in duration of neutropenia in both solid tumor and leukemia patients[4]; however, in this study, we found that a rapid resolution of neutropenia in the G-CSF-treated group was balanced by a higher rate of relapse after cessation of G-CSF effect, leading to similar total durations of neutropenia in the two groups. This is similar to results from Zafrani et al., who found no difference in mean duration of neutropenia in adult kidney transplants treated with G-CSF.[2] An explanation for this could lie in the different etiologies and perspectives of these conditions. Neutropenia in oncology patients is generally due to intermittent dosing of cytotoxic chemotherapies that cause cell death; in this situation, G-CSF stimulates the bone marrow to replace the neutrophils and allow progression to the next stage of chemotherapy, when neutropenic relapse is expected. In solid organ transplant patients neutropenia is often attributed to medications, such as mycophenolate mofetil, trimethoprim–sulfamethoxazole, and valganciclovir, that are dosed continuously and inhibit granulocyte production downstream of G-CSF's effects.[7,8] This difference could account for the slower recovery of ANC reported in our study and other studies of G-CSF use in solid organ transplant[5,9,10] as well as the higher rate of relapse.

The primary goal of treatment of neutropenia with G-CSF is reduction in negative clinical outcomes such as infection, rejection, and hospitalization. In this study, administration of G-CSF was associated with a significantly lower incidence of subsequent hospitalization, though this finding should be interpreted with caution, as hospitalization appeared to be a strong indication for initiation of G-CSF therapy in this cohort. Unfortunately, we do not have data on the reason for most of these hospitalizations, as the majority were not temporally associated with a bacterial infection or rejection episode. Bacterial infections were documented in 10.0% of the overall study population with no differences in the incidence rate between groups. This is similar to data from Winston et al., who found no difference in infection risk among patients randomized to G-CSF use in the early post-transplant course. In contrast, Schmaldienst reported a lower incidence of infection in the treated group, but had a smaller cohort (n = 19) and reported a much more rapid resolution of neutropenia (1.29+/-0.59 days) after G-CSF use in contrast to this and other reported studies.[11] As we found no difference in duration of neutropenia with G-CSF use, it is not surprising that bacterial infection rates were similar. Interestingly, even among afebrile patients with chemotherapy-induced neutropenia, there is no clear role for G-CSF administration in preventing hospitalization or infection[12]; a randomized controlled trial of G-CSF among afebrile oncology patients with ANC <500/mm^3 found no effect on the rate of hospitalization, duration of hospitalization, duration of treatment with antibiotics, or the number of culture-positive infections.[13] In a subgroup analysis, patients in our study with an ANC <500/mm^3 did show a trend toward shorter duration of neutropenia, but this did not reach statistical significance.

Data on rejection in previous studies of G-CSF have diverged. Vrtovec et al. found a lower incidence of rejection in heart transplant recipients treated with G-CSF,[14] while Turegon et al. reported an 8% incidence of rejection within 2 months of G-CSF therapy in kidney transplant recipients,[5] and a randomized controlled trial of G-CSF in liver transplant recipients reported a higher incidence of rejection in the treated group.[15] The incidence of rejection during or within 90 days of neutropenia in this cohort was low, markedly lower than the most recent reports by the North American Pediatric Renal Trials and Collaborative Studies registry,[16] and did not differ based on G-CSF treatment. It is possible that the narrow time range to assess for rejection could have missed neutropenia-associated rejection episodes that were diagnosed later, but the eGFR at one-year post-transplant also did not differ significantly between the two groups. These results are similar to the findings of Hurst et al., who reported no increased risk of allograft loss among 740 adult kidney transplant recipients treated with G-CSF.[3]

This is a large, multicenter study that provides adequate power to examine a variety of clinically important outcomes across a range of local practice patterns. As in any observational study of a therapy, confounding by indication is the chief threat to validity. We adjusted for this using incident rate analysis to examine outcomes in the presence and absence of G-CSF use, adjusted for time-at-risk, as well as sensitivity analyses that excluded pre-G-CSF hospitalization and days of neutropenia. However, adjustment can never completely eliminate the effects of confounding. Additionally, this was a voluntary study; while all neutropenic patients at each participating center were included in the study, transplant centers that do not routinely use G-CSF may have elected not to participate; indeed, only two participating centers in our study did not use G-CSF in any patients. Finally, our study used a broad definition of neutropenia, with resolution defined as an ANC >1500/mm^3, but it is possible that treating physicians are stopping G-CSF after achieving a 'goal' of >500/mm^3 or >1000/mm^3. Further research would be required to know if G-CSF can specifically shorten the duration of moderate or severe neutropenia.

Overall, we did not find any data to support the use of G-CSF to decrease the total duration of neutropenia or prevent bacterial infection, though G-CSF may decrease the risk of subsequent hospitalization. G-CSF use was not associated with an increased risk of rejection or PTLD. These population-level findings do not rule out potential benefit in individual clinical cases, especially when a patient is acutely ill, but prospective randomized studies would be needed to show whether G-CSF use is beneficial in routine use for neutropenic pediatric kidney transplant recipients, especially those with significant neutropenia (ANC <500/mm^3).

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AUTHOR CONTRIBUTIONS

Rachel M Engen participated in research design, performance of the research, data analysis, and writing of the manuscript. Patricia L Weng, Weiwen Shih, Hiren P Patel, Kelsey Richardson, Isa F Ashoor,

Jason Misurac, Avram Z Traum, and Namarata G Jain participated in performance of the research and writing of the manuscript. Shauna L Dowdrick and Michael G Semanik participated in performance of the research. Rajasree Sreedharan participated in research design, performance of the research, and writing of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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