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Effectiveness of G-CSF in Hospitalized Infants with Neutropenia

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Abstract

Objective—To determine the time to hematologic recovery and the incidence of secondary sepsis and mortality among neutropenic infants treated or not treated with granulocyte-colony stimulating factor (G-CSF).

Study Design—We identified all neutropenic infants discharged from 348 neonatal intensive care units in 1997–2012. Neutropenia was defined as an absolute neutrophil count $< 1500/\mu\text{L}$ for 1 day during the first 120 days of life. Incidence of secondary sepsis and mortality and number of days required to reach an absolute neutrophil count $> 1500/\mu\text{L}$ for infants exposed to G-CSF were compared to those of unexposed infants.

Results—We identified 30,705 neutropenic infants, including 2142 infants (7%) treated with G-CSF. Treated infants had a shorter adjusted time to hematologic recovery (HR 1.36, 95% CI 1.30–1.44) and higher adjusted odds of secondary sepsis (OR 1.50, 95% CI 1.20–1.87), death (OR 1.33, 95% CI 1.05–1.68), and the combined outcome of sepsis or death (OR 1.41, 95% CI 1.19–1.67) at day 14 compared to untreated infants. These differences persisted at day 28.

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Conflicts of Interest

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Conclusions—G-CSF treatment decreased the time to hematologic recovery but was associated with increased odds of secondary sepsis and mortality in neutropenic infants. G-CSF should not routinely be used for infants with neutropenia.

Keywords

hematologic recovery; sepsis; prophylaxis

Neutropenia is common in infants, particularly infants who are small for gestational age (SGA) and in the setting of maternal pregnancy-induced hypertension (PIH) or neonatal sepsis.^{1–3} Granulocyte-colony stimulating factor (G-CSF) is a physiologic regulator of neutrophil function that increases neutrophil production and enhances neutrophil activity.⁴ Endogenous production of G-CSF in infants is relatively poor.⁵ Exogenous G-CSF can be used to increase the neutrophil count in neutropenic infants.⁶ This has been done in two settings: as prophylaxis for the prevention of infection in infants with neutropenia⁷ or at high risk for developing neutropenia,⁸ and as adjunctive therapy for septic infants with and without coexisting neutropenia.^{9,10} However, the use of G-CSF in infants for these indications is controversial due to conflicting data regarding its efficacy.

We sought to evaluate the effectiveness of G-CSF in neutropenic, hospitalized infants. The primary outcome was secondary sepsis or mortality at 14 days after the start of G-CSF therapy. The secondary outcomes were secondary sepsis or mortality at 28 days after G-CSF therapy, secondary sepsis at 14 and 28 days after G-CSF therapy, death at 14 and 28 days after G-CSF therapy, and the time to hematologic recovery.

METHODS

Study Population

We identified all infants discharged from 348 neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group in 1997–2012 with ≥ 1 day of neutropenia during the first 120 days of life. The time frame of 1997–2012 was selected *a priori* to maximize the number of infants in our cohort who were treated with G-CSF. Infants with major congenital or chromosomal anomalies including congenital neutropenia syndromes were excluded from the analysis. Data were obtained from an electronic medical record that was generated prospectively and captured information from notes generated by clinicians on all infants cared for by the Pediatrix Medical Group. Information recorded included maternal history and demographics and, on a daily basis, medications, laboratory results, microbiology results, diagnoses, and procedures.¹¹ Timing and method of drug administration and drug dosages were not included in the data available for analysis.

Definitions

Neutropenia was defined as an absolute neutrophil count $< 1500/\mu\text{L}$.¹² Because neutrophil counts were not obtained on a daily basis in most infants and some neutrophil counts prompting G-CSF therapy may have been obtained at other institutions, a neutropenic episode was considered to be treated with G-CSF if an absolute neutrophil count $< 1500/\mu\text{L}$ was documented within the window of 2 days before or 2 days after the first day of G-CSF

exposure. For infants with no measurement obtained on the first day of G-CSF exposure, this window was used as a surrogate for the presence of neutropenia on the start day of G-CSF. Infants with more than one episode of neutropenia were included as follows: when all episodes were treated with G-CSF, the first episode of neutropenia was included; when none of the episodes were treated with G-CSF, the first episode of neutropenia was included; when an infant had both untreated and treated neutropenic episodes, the first episode with G-CSF exposure was included. The episode start day was defined as the first day of G-CSF exposure for episodes treated with G-CSF and the first day of neutropenia for episodes not treated with G-CSF. SGA was defined as previously described.¹³ PIH was considered to be present if there was a maternal diagnosis of eclampsia, preeclampsia, or HELLP (hemolysis, elevated liver enzymes, low platelet) syndrome. Concurrent bacteremia was considered to be present if a positive blood culture was obtained 2 days before or after the episode start day. Blood cultures positive for organisms generally considered to be contaminants (*Bacillus* species, diphtheroids, *Corynebacterium* species) were considered to be negative.¹⁴ Cultures positive for coagulase-negative *Staphylococcus* (CoNS) sepsis were considered positive if they met one of the following criteria: 2 positive blood cultures for CoNS within a 4-day period, 3 positive blood cultures for CoNS within a 7-day period, or 4 positive blood cultures for CoNS within a 10-day period.¹⁵ Cultures growing CoNS that did not meet these criteria were considered to be negative.

Time to hematologic recovery was defined as the number of days from the start day to the first day with an absolute neutrophil count $> 1500/\mu\text{L}$. Secondary sepsis was defined as a positive blood culture from day 3 through days 14 and 28 after the start day. For neutropenic episodes with concurrent bacteremia, secondary sepsis was defined as the presence of a positive blood culture with an organism other than the original organism, or, in cases where a blood culture grew the same organism as the original organism, if there were ≥ 21 days between culture results. Mortality was defined as death occurring from day 3 through days 14 and 28. For infants who died within 2 days of starting G-CSF therapy, mortality was treated as missing.

Statistical Analysis

We compared demographic and baseline characteristics of G-CSF-treated and untreated neutropenic infants. Categorical variables were presented as counts (proportions), and continuous variables were presented as medians (25th and 75th percentiles). We performed chi-square or Fisher's exact tests for comparison of categorical variables and two-sample Wilcoxon rank sum tests for comparison of continuous variables. The time to hematologic recovery between the two groups was compared using a log rank test and a Cox proportional hazards model stratified by gestational age group and adjusted for SGA status, inotropic support, mechanical ventilation, and concurrent bacteremia. Infants without hematologic recovery were censored at the time of discharge. We determined the odds of sepsis, mortality, and the combined outcome at both 14 and 28 days using a multivariable logistic regression analysis adjusted for SGA status, gestational age group, postnatal age at the start day, inotropic support, mechanical ventilation, and concurrent bacteremia. We used a fixed effects model to adjust for potential variation by NICU site. We also calculated the primary outcome using this same adjusted logistic regression model with neutropenia defined as an

absolute neutrophil count $<500/\mu\text{L}$ or with initial absolute neutrophil count as a covariate. We calculated the primary outcome with infants having concurrent bacteremia excluded; the adjustment variables were the same except that concurrent bacteremia was not included. Data were analyzed using STATA 13 (College Station, TX), and a p -value < 0.05 was considered statistically significant. This study was approved by the Duke University Institutional Review Board.

RESULTS

Patient Characteristics

We identified 30,705 infants with neutropenia during the first 120 days of life. Of these, 2142 infants (7.0%) were treated with G-CSF (Table 1). Treated infants had a lower median gestational age and birth weight than untreated infants: 28 weeks (25th and 75th percentile, 26, 31 weeks) vs. 29 weeks (27, 32), $p<0.001$, and 935 g (655, 1451) vs. 1173 g (820, 1720), $p<0.001$, respectively. Compared with untreated infants, more infants treated with G-CSF were SGA (33% vs. 21%, $p<0.001$), had concurrent bacteremia (6% vs. 4%, $p<0.001$), and received ventilator (47% vs. 45%, $p<0.001$) or inotropic support (30% vs. 12%, $p<0.001$). Treated infants were older than untreated infants (median postnatal age 3 days [0, 7] vs. 1 [0, 9], $p<0.001$) and had lower median absolute neutrophil counts, 540/uL (312, 752) vs. 720/uL (495, 874), $p<0.001$. The median platelet counts for both groups were within the normal range on the first day of the neutropenia episode (138,000 vs. 194,000 for treated and untreated infants, respectively). Infants treated with G-CSF were treated for a median of 3 days (1, 3).

Hematologic Recovery

The median hematological recovery times were similar: 2 days (2, 4) and 2 days (2, 3), respectively. However, on Cox proportional hazard analysis, we observed that G-CSF treatment was associated with a shorter time to hematologic recovery, hazard ratio = 1.36, 95% CI 1.30–1.44 (Figure).

Sepsis and Mortality

Nine percent (192/2142) of treated infants and 6% (1772/28,563) untreated infants had a positive blood culture during the study period (Table 2). Sepsis occurred a median of 17 days (8, 35) after the start of the study period. On multivariable logistic regression, we observed an increase in sepsis, death, and the composite outcome within 14 days of the start day for G-CSF-treated infants compared with untreated infants. These differences persisted at 28 days. Sensitivity analyses that defined neutropenia as an absolute neutrophil count $<500/\mu\text{L}$ or added the initial absolute neutrophil count as an adjustment covariate did not change the association of G-CSF exposure with an increased odds of death or sepsis at 14 days, odds ratio = 1.54, 95% CI 1.18, 2.01, and odds ratio = 1.34, 95% CI 1.13, 1.60, respectively. A second sensitivity analysis found that treatment with G-CSF exposure was still associated with an increased odds of death or sepsis at 14 days when infants with bacteremia at the start of the neutropenic period were excluded, odds ratio = 1.36, 95% CI 1.14, 1.62. Sepsis occurred while receiving G-CSF in 22 (0.1%) infants.

DISCUSSION

This study represents the largest evaluation of G-CSF use in neutropenic infants to date. In our study population, 7% of the neutropenic infants received G-CSF. In this cohort, G-CSF appeared to be used preferentially in infants with more severe illness because infants treated with G-CSF were younger, smaller, had lower Apgar scores, and more often required ventilator and inotropic support. Although the time to hematologic recovery was shorter in infants with G-CSF treatment, treated infants were more likely than untreated infants to develop secondary sepsis or die in the 14- and 28-day periods following their neutropenic episode even after adjustment for gestational age, SGA status, inotropic support, mechanical ventilation, and concurrent bacteremia.

Underlying causes of neonatal neutropenia are difficult to determine, and multiple factors may play a role. Blood dyscrasias did not appear to a prominent cause of neutropenia in our cohort; median platelet counts for both groups were >130,000. Prematurity and maternal PIH are important predisposing factors for neonatal neutropenia.^{16,17} This appears to be due to decreased neutrophil production during the first few days of life.^{3,18} On average, 40–80% of infants exposed to PIH develop neutropenia.^{1,19} For infants <1000 g birth weight, 68% of early neutropenia has been attributed to PIH.²⁰ The majority of neutropenia related to PIH resolves within the first 3 days of life.^{20,21} Infants who are SGA are also more likely to develop neutropenia than those who are not SGA.²² In our cohort, more infants treated with G-CSF were SGA or were born to mothers with PIH than those not treated with G-CSF.

PIH-related neutropenia has been associated with an increased risk of secondary infection.^{3,23} This concern forms the basis for prophylactic use of G-CSF in neutropenic infants. A study of 28 infants with prolonged PIH-related neutropenia comparing the incidence of sepsis during the first 28 days of life found that treatment with G-CSF reduced the incidence of sepsis to 13% (2 of 15 infants) compared to 54% (7/13) in untreated infants, $p < 0.05$.²⁴ In infants <32 weeks gestation, use of a similar product, granulocyte-macrophage colony stimulating factor (GM-CSF), led to a slightly decreased incidence of sepsis in the 2 weeks following study enrollment compared to untreated infants, 11/36 vs. 18/39, OR 0.51, 95% CI 0.20–1.31.⁸ GM-CSF has been shown to increase the activity of neutrophils and macrophages, in addition to increasing neutrophil numbers, and for this reason has been theorized to be more effective than G-CSF as adjunctive therapy for sepsis.²⁵ A study of non-neutropenic infants with presumed early onset sepsis found that that infants treated with G-CSF had increased ANCs and shortened hospital length of stay.²⁶

Two other studies noted that the incidence of additional infections decreased when G-CSF was used during a sepsis episode occurring earlier in life, suggesting that G-CSF could be effective as prophylaxis for the prevention of infection.^{25,28} A multicenter randomized trial found that 102 neutropenic infants <32 weeks gestational age given prophylactic G-CSF had higher infection-free survival at 2 weeks compared to 98 untreated infants (84% vs. 71%, $p = 0.03$). However, this difference was not present at 4 weeks (73% vs. 67%, $p = 0.42$).⁷ Another multicenter, randomized trial of 280 infants <32 weeks gestational age found that although infants with neutropenia resolved their neutropenia more quickly when given GM-CSF compared with control infants, there was no difference in sepsis-free survival between

treated and untreated infants, 67% vs. 74%.²⁹ Paradoxically, there was a trend toward an increased incidence of sepsis in the group of infants treated with GM-CSF compared to untreated infants at both 14 (24% vs. 19%, respectively) and 28 days (30% vs. 24%, respectively).²⁹ Similarly, we also observed an increase in sepsis in our cohort of infants treated with G-CSF.

Neutropenia may not only predispose infants to sepsis but may also arise as a result of sepsis. A study of 168 septic infants found that neutropenia was present in 38% of cases.² Septic infants with neutropenia may have worse outcomes than their non-neutropenic septic peers.³⁰ Several studies conducted to assess the usefulness of G-CSF as an adjunctive therapy for infants with sepsis-related neutropenia have demonstrated that G-CSF administration is effective at increasing the absolute neutrophil count in septic infants.^{10,21,26,28} Three small studies also suggested a reduction in mortality for septic infants with neutropenia following G-CSF administration. In one study, infants treated with G-CSF had a trend toward improved survival compared to historical controls, 12/14 (86%) vs. 15/24 (62%), $p=0.1$.³¹ In another study, a significant difference in survival was seen in the 28 days after a sepsis episode, with 13/14 (93%) of G-CSF-treated infants and 5/11 (45%) of conventionally treated infants surviving, $p<0.03$.²¹ A phase 1 study found that a greater proportion of septic infants treated with G-CSF survived to 6 months, 12/13 (92%), than those given placebo, 8/15 (53%), $p=0.04$.⁹ Conversely, another small study found that G-CSF administration to neutropenic infants with clinical sepsis did not improve survival compared to routine care, 8/10 vs. 7/10, respectively.³² A larger study found that neutropenic infants with suspected or confirmed sepsis who were treated with G-CSF had similar mortality compared to those given only antibiotics, 10/33 (30.3%) vs. 6/23 (26.6%).³³ A study of 3644 SGA infants found that neutropenia was not independently associated with late onset sepsis, odds ratio =1.44, 95% CI 0.73, 2.61.²² With a much larger sample size, we also found that neutropenic infants had increased odds of death following treatment with G-CSF compared with untreated infants. However, the actual cause of death for infants who died is unknown, so we cannot hypothesize about the mechanism by which G-CSF exposure may be associated with increased odds of death. Additionally, it is possible that G-CSF exposure is a surrogate marker for other unmeasured confounders.

Although our study is the largest evaluation of G-CSF safety and outcomes in neutropenic infants to date, there are several important limitations to our findings. We included only one episode of neutropenia for each infant, and the role of G-CSF in recurrent neutropenia was not assessed. Because neutrophil counts were obtained at the discretion of the clinician, the median time to hematologic recovery could not be calculated on all infants and may be overestimated in some infants. Dosing information was not available; thus, we were not able to account for dose-dependent differences in outcomes. Finally, infants in our study were not randomized to receive G-CSF or not. G-CSF was prescribed at the discretion of the clinicians, and we were not able to determine what motivated clinicians to start G-CSF in some infants with neutropenia and not in others. Although we attempted to control for these important confounders and others in our analysis, it is likely that unmeasured confounders remain and may account for some of the differences noted between the treated and untreated infants.

In conclusion, we found that G-CSF treatment reduced the time to hematologic recovery but was associated with higher mortality and secondary sepsis in treated infants. Since prior studies have had conflicting efficacy findings and there is the possibility of harm, G-CSF should not routinely be used for infants with neutropenia.

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APPENDIX

The Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee

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Abbreviations

G-CSF	granulocyte-colony stimulating factor
GM-CSF	granulocyte-macrophage colony stimulating factor
NICU	neonatal intensive care unit
PIH	pregnancy-induced hypertension
SGA	small for gestational age

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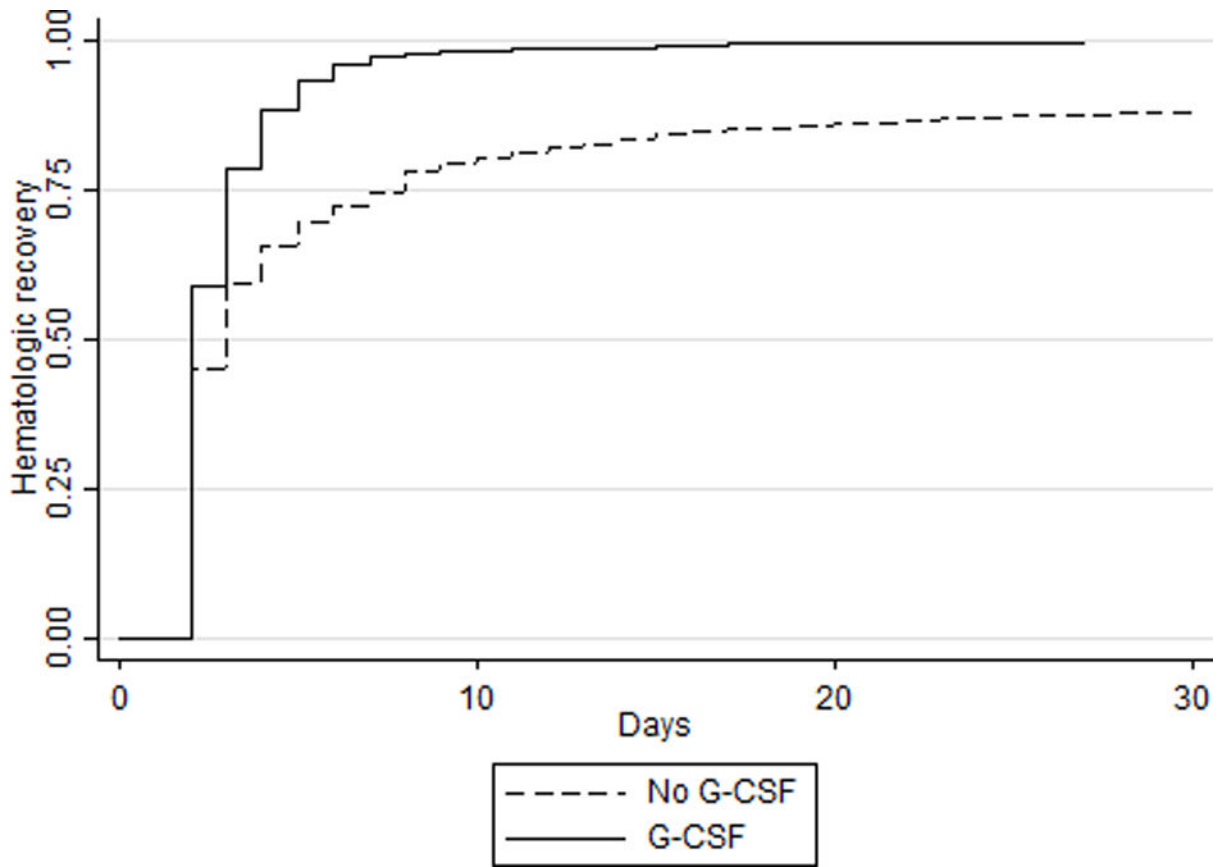


Figure 1.
Time to hematologic recovery for neutropenic infants.

Table 1

Demographics

	G-CSF	No G-CSF
	N=2142 (%)	N=28,563 (%)
Gestational age, weeks		
<26	480 (22)	4544 (16)
26–28	751 (35)	7942 (28)
29–32	524 (24)	9448 (33)
33–36	230 (11)	4230 (15)
37	155 (7)	2377 (8)
Birth weight, g		
<1000	1170 (55)	10,929 (38)
1000–1499	463 (22)	8169 (29)
1500–2499	326 (15)	6536 (23)
2500–3499	137 (6)	2150 (8)
3500	45 (2)	751 (3)
Postnatal age, days		
7	20,768 (73)	1538 (72)
8–30	3584 (13)	358 (17)
>30	4211 (15)	246 (11)
5-min Apgar score		
0–3	110 (5)	1255 (5)
4–6	448 (21)	4304 (15)
7–10	1533 (73)	22312 (80)
Race		
White	1037 (50)	13,360 (48)
Black	526 (25)	7564 (27)
Hispanic	401 (19)	5305 (19)
Other	108 (5)	1410 (5)
Small for gestational age	696 (33)	6099 (21)
Male	1311 (61)	16948 (59)
Cesarean section	1548 (73)	20436 (72)
Maternal hypertension*	356 (17)	4296 (15)
Inotropic support [†]	640 (30)	3562 (12)
Ventilator support [†]	1443 (47)	12,745 (45)
Concurrent bacteremia	134 (6)	1007 (4)

* Maternal hypertension includes preeclampsia, eclampsia and HELLP (hemolysis, elevated liver enzymes, low platelet) syndrome.

[†] On the first day of neutropenia (untreated group) or first day of G-CSF therapy (treated group).

Table 2

Outcomes

	G-CSF	No G-CSF	Adjusted Odds Ratio* (95% Confidence Interval)
	N=2142 (%)	N=28,563 (%)	
Secondary sepsis			
3–14 days	127 (6)	1072 (4)	1.50 (1.20–1.87)
3–28 days	192 (9)	1772 (6)	1.31 (1.09–1.57)
Death			
3–14 days	124 (6)	776 (3)	1.33 (1.05–1.68)
3–28 days	157 (7)	1073 (4)	1.32 (1.07–1.62)
Death or secondary sepsis			
3–14 days	235 (11)	1779 (6)	1.41 (1.19–1.67)
3–28 days	321 (15)	2712 (9)	1.29 (1.10–1.50)

* Odds of outcome for G-CSF group compared to non-G-CSF group adjusted for gestational age at birth, postnatal age, small for gestational age status, inotropic support, ventilator support, and concurrent bacteremia.