Late-Onset Neutropenia in Very Low Birth Weight Infants

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ABSTRACT. *Background.* **Neutropenia, defined as absolute neutrophil count (ANC) <1500/mm³, affects 6% to 58% of premature infants in the first week of life. This early-onset neutropenia in premature infants has previously been correlated with sepsis, maternal hypertension, severe asphyxia, and periventricular hemorrhage. Late-onset neutropenia, defined as ANC <1500/mm³ at a postnatal age of ≥3 weeks, has not been previously reported.**

Objectives. **The purposes of this study were to determine the prevalence of late-onset neutropenia in very low birth weight (VLBW) infants and to examine the factors that may be associated with this phenomenon.**

Methods. **A weekly complete blood cell count (CBC) was performed routinely in all premature infants with birth weight ≤1500 g (n = 225) admitted to the neonatal intensive care in a 3-year period who survived until discharge. CBC and differentials were recorded at day 1, day 3, and then weekly until discharge. The clinical data of the study infants were collected by reviewing the medical records retrospectively.**

Results. **Late-onset neutropenia was detected in 51 infants (22%). In both neutropenic (n = 51) and nonneutropenic infants (n = 174), ANC increased postnatally, remained above 5000/mm³ for the first 3 weeks of life, and had a marked decrease at ~4 weeks of age. Thereafter, ANC decreased to a level of ~1400/mm³ in the neutropenic infants and 4000/mm³ in the nonneutropenic infants. The neutropenic infants had a significantly lower nadir ANC, lower hemoglobin, and higher reticulocyte count than did the nonneutropenic infants with similar platelet counts. None of the study infants received erythropoietin during their hospitalization. This late-onset neutropenia occurred at postnatal age of 6 ± 2 weeks (range: 3–10 weeks). The duration of neutropenia was 1.7 ± .7 weeks (range: 1–3 weeks). All of the neutropenic infants had anemia of prematurity with high reticulocyte count and normal platelet count. The neutropenic infants were stable, growing on full oral feedings, and had no signs or symptoms of sepsis. No adverse effects of late-onset neutropenia were apparent in these infants.**

Conclusion. **Late-onset neutropenia is a common incidental finding in stable, growing VLBW infants that has not been previously reported. Late-onset neutropenia is a phenomenon that occurs in anemic premature infants who have marked reticulocytosis. Normal regulation of hematopoiesis is accompanied by a balance between colony-stimulating factors, such as erythropoietin and granulocyte colony-stimulating factor, which regulate erythropoiesis and granulopoiesis. We speculate that imbalance of these factors with increased reticulocytopoiesis in response to anemia of prematurity may explain this phenomenon. We recommend avoiding institution of aggressive, potentially harmful therapy for this phenomenon in healthy, growing VLBW infants.** *Pediatrics* **2000;106(4). URL: http://www.pediatrics.org/cgi/content/full/106/4/e55;** ***neutropenia, absolute neutrophil count, very low birth weight, infants, sepsis.***

ABBREVIATIONS. CBC, complete blood cell count; ANC, absolute neutrophil count; VLBW, very low birth weight; SGA, small for gestational age; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; WBC, white blood cell count; SEM, standard error of the mean; G-CSF, granulocyte colony-stimulating factor.

The complete blood cell count (CBC) with differential is the most common screening test performed in the evaluation of infants admitted to the neonatal intensive care unit. Recognition of significantly abnormal CBC and differential values requires adequate normative data to be available for comparison. The use of absolute neutrophil count (ANC) has improved early recognition and sensitivity in screening for neonatal bacterial sepsis.[1–4] Several investigators have suggested reference values for neutrophil cell counts in premature infants during the first 28 days of life.[1–9] This published data may be inadequate when dealing with stable, growing premature infants >28 days of age. Neutrophils are important as a host defense against bacterial infection.[10] When the neutrophil supply is inadequate, neutropenia can develop and the possibility of surviving an infection decreases.[2,11,12] Neutropenia, defined as ANC <1500/mm³, affects 6% to 58% of premature infants in the first week of life.[13–15] This early-onset neutropenia has been reported to occur within the first week of life, with one half of the total episodes starting on the first day of life and approximately two thirds of all episodes lasting <1 week.[13] Christensen, Manroe, and others[1,16–20] had proposed several explanations for this early-onset neutropenia. Premature infants may have a decreased neutrophil storage pool and may exhaust their reserve of neutrophils quickly.[20] Neutropenia can be a sign of inadequate neutrophil production or increased consumption.[16,17] In addition, neutropenia can occur even in the presence of normal neutrophil supply, as during margination of circulating neutrophils.[21] Thus, the detection of neutropenia does not signify

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This work was presented in part at the Society for Pediatric Research Meeting; May 1–4, 1999; San Francisco, CA.

Received for publication Feb 14, 2000; accepted Apr 25, 2000.

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that the host defense is compromised or that the neutrophil supply is diminished.

Early-onset neutropenia in premature infants has previously been correlated with sepsis, maternal hypertension, severe asphyxia, and periventricular hemorrhage.[1,8,13,14,17–19,22–25] Manroe et al[1] identified neutropenia as the single most accurate predictor of infection in newborn infants. Early-onset neutropenia in premature infants may be associated with an increase in the incidence of early-onset sepsis[26] and nosocomial infection.[8,19]

Late-onset neutropenia in stable, growing premature infants, defined as ANC $<1500/mm^3$ at a postnatal age of ≥ 3 weeks, has not been previously reported. The purposes of this study were to determine the prevalence of late-onset neutropenia in very low birth weight (VLBW) infants (≤ 1500 g) and to examine the factors that may be associated with this phenomenon.

METHODS

All premature infants (≤ 1500 g) who were admitted consecutively to the neonatal intensive care unit at Sparrow Hospital, Lansing, Michigan, between July 1995 and August 1998 were enrolled in this study. The institutional review board of the hospital approved the study. A weekly CBC and differential was performed routinely in all of these infants during their hospitalization. Infants who expired during hospitalization or were transported to other centers or had congenital anomalies were excluded from the study. Medical records of the remaining premature infants were reviewed retrospectively for birth weight, gestational age, Apgar scores, sex, race, small for gestational age (SGA), respiratory distress syndrome (RDS), ventilator support, oxygen therapy, intraventricular hemorrhage (IVH), history of sepsis, prenatal and postnatal steroids, blood transfusions, age to reach full oral feeding, duration of iron therapy, discharge weight, and length of hospitalization. CBC and differentials were recorded at day 1, day 3, and then weekly until discharge. All blood samples for CBC were drawn either from an umbilical catheter or from a peripheral puncture if an umbilical catheter was no longer present. The majority of the CBC values in the study infants after the third week of life were obtained from heel sticks. White blood cell counts (WBCs) were performed using a Coulter-Stks Analyzer (Beckman Coulter Inc, Miami, FL) then the differentials were analyzed automatically. The laboratory technician then individually reviewed the smears and counted the differential manually. The ANC was determined by multiplying the total WBC by the percentage of neutrophils. Neutrophils were corrected for the nucleated RBCs. Late-onset neutropenia was defined as ANC $<1500/mm^3$ at a postnatal age of ≥ 3 weeks. Other hematologic data (such as hematocrit, platelet, and reticulocyte count) were recorded. During discharge planning and in coordination with the pediatricians, infants who had late-onset neutropenia at the time of hospital discharge had follow-up CBCs performed until their neutropenia was resolved. In addition, if any of the neutropenic infants was rehospitalized within 6 months after discharge, the medical records were reviewed to identify the cause of their hospitalization.

Statistical Analysis

Data are presented as mean ± standard error of the mean (SEM) unless stated otherwise. Student's t test, χ^2 test, Mann-Whitney rank-sum test, and 2-way analysis of variance with repeated-measures of 1 factor were used for statistical analysis. A P value of $<.05$ was considered to indicate statistical significance.

RESULTS

During the study, 277 infants with a birth weight ≤ 1500 g were admitted to the neonatal intensive care unit. Fifty-two infants were ineligible: 36 expired, 10 were transported to other centers, and 6 had congenital anomalies. The number of infants who were eligible and who were included in the study was 225 infants. After collecting the data, the infants were divided into 2 groups: infants who developed neutropenia (n = 51; 22%) and infants who did not develop neutropenia (n = 174; 78%).

ANC increased postnatally in both neutropenic and nonneutropenic infants and remained above $5000/mm^3$ for the first 3 weeks of life and had a marked decrease at ~4 weeks of age (Fig 1). Subsequently, the neutrophil counts decreased to a level of $\sim 1400/mm^3$ in the neutropenic infants and $4000/mm^3$ in the nonneutropenic infants. The hematocrit was high initially and started to decrease gradually in both groups. The hematocrit tended to be lower in the neutropenic infants (Fig 2). Reticulocyte count was high initially in both groups and decreased by week 2 of life. Reticulocyte count started to increase in both groups by week 4 of life and was significantly

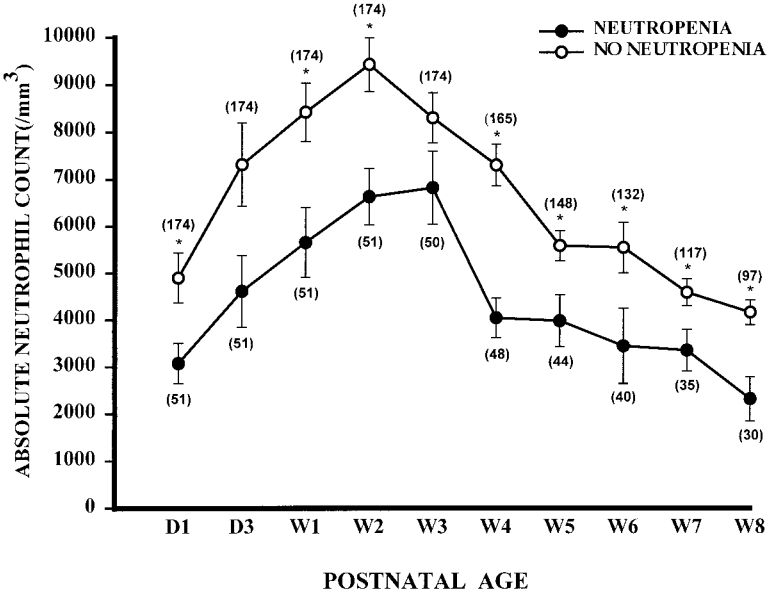

Fig 1. ANC ($/mm^3$) of the neutropenic and nonneutropenic infants. Numbers in parenthesis represent the number of infants that had CBC at that data point. Error bars represent mean ± SEM. *$P < .05$ versus nonneutropenic infants.

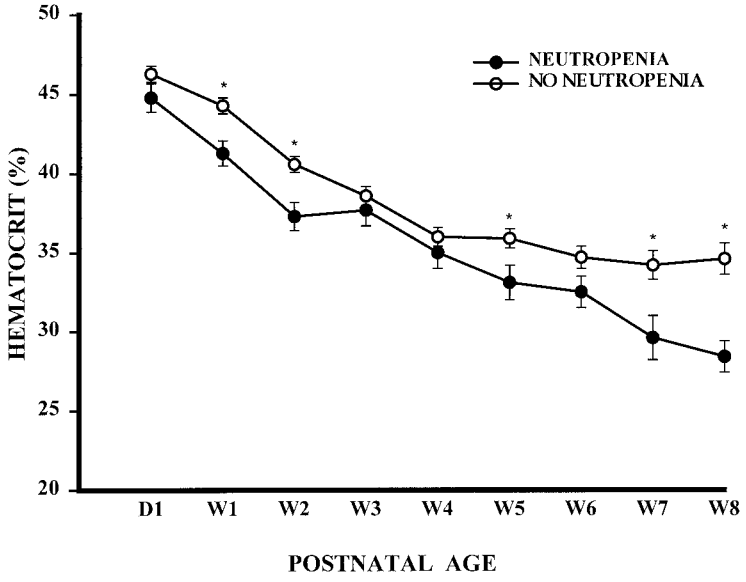

Fig 2. The hematocrit (%) of the neutropenic and nonneutropenic infants. Error bars represent mean ± SEM. *$P < .05$ versus nonneutropenic infants.

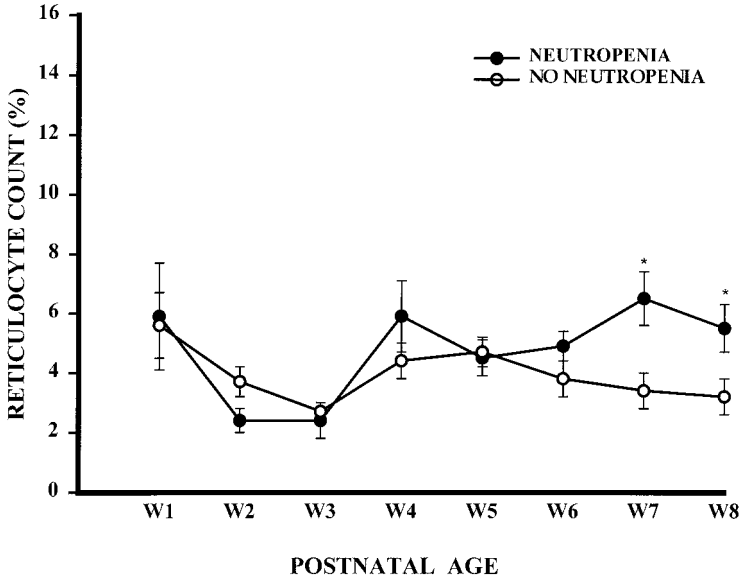

Fig 3. The reticulocyte count (%) of the neutropenic and nonneutropenic infants. Error bars represent mean ± SEM. *$P < .05$ versus nonneutropenic infants.

higher in the neutropenic infants by week 7 of life (Fig 3). There was no difference in platelet count between the 2 groups (Fig 4). Late-onset neutropenia occurred at a postnatal age of 6 ± 2 weeks (range: 3–10 weeks), and the duration of neutropenia was 1.7 ± .7 weeks (range: 1–3 weeks). Our ability to detect the exact duration is limited because of early hospital discharge. Some infants were discharged as early as the third week of life in both groups. So, the incidence of late-onset neutropenia may have been higher if the nonneutropenic infants had been followed beyond hospital discharge. All the neutropenic infants had anemia of prematurity with hemoglobin of 9.7 ± 1.1 g/dL (range: 6.7–11.8 g/dL), high reticulocyte count of 5.4% ± 2.1% (range: 3%–10.4%), and normal platelet count (391 ± 128 $\times 10^3/mm^3$). None of the study infants received erythropoietin during their hospitalization. The neutropenic infants were stable, growing on full oral feedings, and had no signs or symptoms of sepsis. No adverse effects of late-onset neutropenia were apparent in these infants. There was no difference between the infants who developed late-onset neutropenia ($n = 51$) and those who did not ($n = 174$) in gestational age (28 ± 2 weeks vs 28 ± 2 weeks), birth weight (1011 ± 265 g vs 1088 ± 270 g), Apgar scores, race, sex, and the number of infants who were SGA (Table 1). Also, there was no difference between the groups in incidence of RDS, duration of mechanical ventilation, oxygen therapy, incidence of patent ductus arteriosus, IVH, sepsis, exposure to antenatal and postnatal steroids, the need for blood transfusion, age to reach full oral feedings, duration of iron therapy, the incidence of early-onset neutropenia, discharge weight, and the length of hospitalization. Neutropenic infants had a significantly lower nadir ANC than did nonneutropenic infants (1067 ± 44/mm^3 vs 4062 ± 113/mm^3; $P < .001$), lower hemoglobin (9.7 ± .2 g/dL vs 21.2 ± .1 g/dL; $P < .001$), higher reticulocyte count (6.1% ± .4% vs 4.9% ± .3%; $P < .01$) but similar platelet counts (391 ± 19/mm^3 vs 944 ± 18/mm^3; P = not significant).

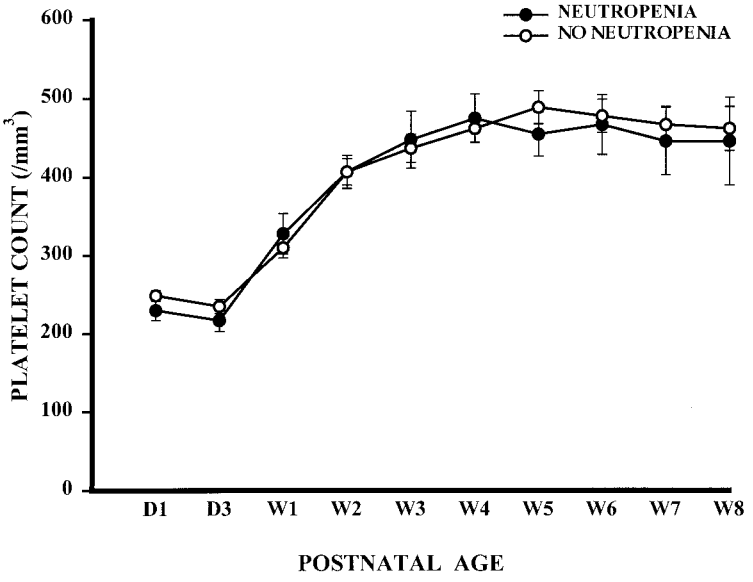

Fig 4. The platelet count (/mm^3) of the neutropenic and nonneutropenic infants. Error bars represent mean ± SEM. There was no significant difference between the 2 groups.

Fifty percent of the infants with late-onset neutropenia (26/51) had their ANC increased to a level above 1500/mm^3 before their hospital discharge, while 24 infants had their ANC increased to that level within 1 month after discharge. One infant had intermittent neutropenia that recovered by 2 months after discharge. Seventeen percent of the infants with late-onset neutropenia (9/51) were rehospitalized within 6 months after discharge. Seven infants were hospitalized for hernia repair, 2 infants for apnea, and none of them had sepsis or neutropenia. All of these infants were rehospitalized to our regional children's medical center.

DISCUSSION

Late-onset neutropenia that occurs in stable, growing premature infants has not been previously reported. In this review, late-onset neutropenia occurred in 22% of VLBW infants. Even when neutropenia was defined as ANC <1000/mm^3, the incidence was still as high as 10% of the study infants (22/225 infants). This late-onset neutropenia occurred at ≥3 weeks of age, in the absence of the known risk factors for this phenomenon, and lasted for 1 to 3 weeks. Our ability to detect the exact incidence and duration of this type of neutropenia is limited because of the early hospital discharge of some infants. The incidence and duration may even be higher if the CBCs were followed for a longer time in those infants who were discharged from the hospital early.

Koenig and Christensen[19] and Xanthou[2] have shown significant relationship between gestational age, birth weight, and increased susceptibility of VLBW infants to neutropenia. There was no difference between the neutropenic and nonneutropenic infants in gestational age and birth weight as shown in Table 1. Additionally, none of these neutropenic episodes were attributable to isoimmune neutropenia or postexchange transfusion neutropenia as has been shown in early-onset neutropenia.[13,14] Gessler et al[15] have previously shown that there was a high incidence of neutropenia in premature infants after 1 week of therapy with certain antibiotics. The number of infants who had sepsis that required a full course of antibiotics was similar in both neutropenic and nonneutropenic infants. In addition, none of the neutropenic infants in our study were on antibiotics for at least 2 to 3 weeks before detection of late-onset neutropenia. Halperin et al[27] have shown that erythropoietin therapy in premature infants can be complicated by development of neutropenia. None of the infants in our study were treated with erythropoietin.

The exact mechanism responsible for the reduced ANC in our patients is not known. The neutropenic infants in our study were anemic with significantly lower hemoglobin and higher reticulocyte count, compared with nonneutropenic infants. Previously, Manroe et al[1] observed a similar phenomenon and found that newborn infants who developed neutropenia had reticulytosis occurring at 14 days of postnatal age. In addition, Shannon et al[28] observed an inverse relationship between reticulocytic and neutrophil counts in premature infants. Normal regulation of hematopoiesis is accompanied by a balance between colony-stimulating factors, such as erythropoietin and granulocyte colony-stimulating factor (G-CSF), which regulate erythropoiesis and granulopoiesis.[29–31] We postulate that late-onset neutropenia may be the result of a decrease in neutrophil-specific differentiation or growth factors imbalance or combinations of the 2.

The studies of Chen, Nicola, and others[32–35] have suggested a mechanism for down-modulation of neutrophil production in newborns with neutropenia. These investigators observed that when 1 type of hematopoietic growth factor becomes bound to its cell-surface receptors, receptors for other hematopoietic growth factors may be down-regulated. Thus, the receptors on hematopoietic progenitors that are specific for neutrophilic growth factors may undergo down-modulation by the previous interaction of the

TABLE 1. Characteristics of the Study Infants

Characteristic	Neutropenia $n = 51$ (22%)	No Neutropenia $n = 174$ (78%)
Gestational age (wk)	28 ± 1	28 ± 1
Median (range)	28 (23–33)	28 (24–34)
SGA	8 (16%)	25 (14%)
Birth weight (g)	1011 ± 38	1088 ± 21
Median (range)	928 (534–1465)	1086 (510–1500)
Sex		
Male	31 (60%)	101 (58%)
Female	20 (40%)	73 (42%)
Race		
White	37 (72%)	129 (74%)
Black	10 (20%)	31 (18%)
Others	4 (8%)	14 (8%)
Apgar scores		
5-min (median)	7	8
Infants with Apgar scores <6 at 5 min	4 (8%)	19 (11%)
RDS	35 (69%)	125 (72%)
Ventilator support (d)	14 ± 2	15 ± 1
Median (range)	7 (0–70)	5 (0–64)
Oxygen therapy (d)	24 ± 3	29 ± 2
Median (range)	16 (0–99)	19 (0–123)
IVH (grade I–IV)	4 (8%)	22 (12%)
Steroids		
Prenatal	28 (55%)	92 (53%)
Postnatal	18 (35%)	57 (33%)
Blood transfusion	42 (82%)	142 (80%)
Iron therapy (d)	30 ± 2	27 ± 2
Median (range)	29 (10–48)	27 (4–58)
Age to reach full oral feeding (d)	16 ± 1	18 ± 1
Median (range)	14 (3–37)	14 (2–78)
Early-onset neutropenia	13/51 (25%)	38/174 (22%)
Length of hospitalization (d)	60 ± 3	58 ± 2
Median (range)	58 (24–98)	55 (25–120)
History of sepsis	15/51 (30%)	61/174 (35%)
Discharge weight (g)	1998 ± 28	2036 ± 18
Median (range)	2030 (1526–2382)	2023 (1523–2911)

Numbers represent mean ± SEM. There was no difference between the 2 groups in any of the values indicated. IVH was classified according to the classification of Papile et al.[49] The decision to treat premature infants with iron was made by the attending neonatologist. Premature infants with anemia of prematurity who are in full feeding were given 4 to 6 mg/kg/day of elemental iron orally.

receptors with other hematopoietic growth factors such as erythropoietin.

One other possible mechanism for the development of late-onset neutropenia is imbalance of hematopoietic growth factors that regulate hematopoiesis.[29,36–38] Christensen et al[29] previously observed that human fetal progenitor cells exposed to extraordinarily high concentrations of erythropoietin had a down-modulation of neutrophil production. Koenig and Christensen[24] have also observed that newborns with concurrent Rh hemolytic disease and neutropenia have a very high level of erythropoietin and a marked increase in erythropoiesis. These investigators speculated that erythropoiesis in these neutropenic infants may be accompanied by a down-modulation of neutrophil production.[24] Other investigators have shown spontaneous increase in endogenous production of erythropoietin associated with reticulocytosis in premature infants.[39] Therefore, we speculate that the majority of progenitor cells that are available for hematopoiesis may be consumed during the enhanced erythropoiesis secondary to anemia of prematurity and may limit their availability for granulopoiesis. This may lead to a decrease in neutrophil production, failure of neutrophil storage pool mechanisms to replace the consumed neutrophils, and ultimately a lower ANC and neutropenia.[16,17] We did not measure erythropoietin or other cytokine concentrations in the present study. Whatever the causative mechanism, we propose that this type of neonatal neutropenia may be the result of a transient decrease in neutrophil production during erythropoiesis.

The ANCs in our study infants (Fig 1) have a similar trend to neutrophil counts in previous studies.[1,3,8,15] The postnatal changes in hematocrit and reticulocyte counts may help to explain the mechanism of this trend. The high hematocrit and reticulocyte counts in premature infants at birth are manifestations of the high erythropoiesis in utero.[39] Subsequently, during the first 3 to 4 weeks of life, premature infants received multiple blood transfusions to maintain their hematocrit. Blood transfusions have been shown to be associated with a decrease in erythropoiesis.[36] This may lead to an increase in the availability of progenitor cells for granulopoiesis and ultimately to a postnatal increase in the ANC in both neutropenic and nonneutropenic infants (Fig 1). The decrease in ANC at ~4 weeks of age was probably attributable to the decrease in blood transfusion requirements, lower hematocrit,

and enhancement of erythropoiesis with subsequent decrease in granulopoiesis as discussed earlier.

ANCs tended to be lower in the neutropenic than in the nonneutropenic infants from day 1 of life. There is no clear explanation for this tendency and it seems that this tendency could be a variance of normal, because both groups of infants were similar in the severity of their illness (Table 1). In addition, birth weight, number of infants who were SGA, age to reach full oral feeding, and discharge weight were similar in both groups (Table 1).

During the first 3 to 4 weeks of life, premature infants are critically ill with multiple foreign bodies, such as endotracheal tubes, central or peripheral lines that increase their susceptibility to infection, especially if they have early-onset neutropenia. G-CSF increases proliferation of progenitor cells and enhances the cell function of neutrophils.[40,41] Multiple studies have shown a possible beneficial effect of the use of G-CSF in premature infants, especially those with early-onset neutropenia.[42–48] We doubt that such a therapy would be of any benefit for premature infants with late-onset neutropenia. These infants are usually stable without the risk factors that may increase their susceptibility to infection. In addition, 50% of the infants with late-onset neutropenia had their ANC increased to a level above 1500/mm^3 before discharge, while the remaining neutropenic infants had their ANC increased to that level within 1 month after hospital discharge, with the exception of 1 infant who had intermittent neutropenia that recovered by 2 months after discharge. All of these neutropenic infants were stable, growing, and had no signs or symptoms of sepsis. Late-onset neutropenia is probably a benign developmental phenomenon in VLBW infants with anemia of prematurity and reticulocytosis. The number of infants with late-onset neutropenia was 51, which is too small to statistically power the possibility that nosocomial infection is absent in these infants. We recommend avoiding the institution of aggressive therapy such as G-CSF for this phenomenon until further studies are performed to examine the incidence of nosocomial infection in stable, growing VLBW infants with late-onset neutropenia.

The ANC in our study infants, especially in the neutropenic infants, were below the lower limit of the reference values established by Manroe et al[1] and Xanthou[2] but were similar to the reference values established by Mouzinho.[3] These reference values were based on data obtained during the first 28 days of life.[1–3] The high incidence of late-onset neutropenia suggests the need for development of reference ranges for neutrophil counts among VLBW infants >28 days of age. In addition, further investigation will be needed to clarify the exact mechanism responsible for the development of late-onset neutropenia in stable, growing VLBW infants.

ACKNOWLEDGMENTS

We acknowledge the professional assistance of Valorie Kinne and Debbie Torok during the preparation of this manuscript.

We also thank Dr Carole Beno for her constructive criticism and review.

REFERENCES

1. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. *J Pediatr*. 1979;95:89–98
2. Xanthou M. Leukocyte blood picture in healthy full-term and premature babies during neonatal period. *Arch Dis Child*. 1970;45:242–249
3. Mouzinho A. Revised reference ranges for circulating neutrophils in very low birth weight neonates. *Pediatrics*. 1994;94:76–82
4. Coulombel L, Denhan M, Tchernia G, et al. The number of polymorphonuclear leukocytes in relation to gestational age in the newborn. *Acta Paediatr Scand*. 1979;68:709–711
5. Davies NP, Buggins AGS, Snijders RJM, et al. Blood leukocyte count in the human fetus. *Arch Dis Child*. 1992;67:399–403
6. Lloyd BW, Oto A. Normal values for mature and immature neutrophils in very preterm babies. *Arch Dis Child*. 1982;57:233–235
7. Nash PL, Kwon IG. CBC and differential in VLBW infants. *Neonatal Network*. 1998;17:17–21
8. Cadnapaphornchai M, Faix RG. Increased incidence of nosocomial infection in neutropenic low birth weight (2000 g or less) infants of hypertensive mothers. *J Pediatr*. 1992;121:956–961
9. Christensen RD. Expected hematologic values for term and preterm neonates. In: Christensen RD, ed. *Hematologic Problems of the Neonate*. Philadelphia, PA: WB Saunders Co; 2000:117–136
10. Miller ME. *Host Defenses in the Human Neonate*. New York, NY: Grune and Stratton Inc; 1978:59–71
11. Hutter JJ, Hathaway WE, Wayne ER. Hematologic abnormalities in severe neonatal necrotizing enterocolitis. *J Pediatr*. 1976;88:1026–1031
12. Bodey GP, Buckley M, Sathe YS, et al. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med*. 1966;64:328–340
13. Baley JE, Stork EK, Warkentin PI, Shurin SB. Neonatal neutropenia: clinical manifestations, cause and outcome. *Am J Dis Child*. 1988;142:1161–1165
14. Engle WD, Rosenfeld CR. Neutropenia in high-risk neonates. *J Pediatr*. 1984;105:982–986
15. Gessler P, Luders R, Konig S, Haas N, Lasch P, Kachel W. Neonatal neutropenia in low birth weight premature infants. *Am J Perinatol*. 1995;12:34–38
16. Christensen RD, Rothstein G. Exhaustion of mature marrow neutrophils in neonates with sepsis. *J Pediatr*. 1980;96:316–318
17. Al-Mulla ZS, Christensen RD. Neutropenia in the neonate. *Clin Perinatol*. 1995;122:711–739
18. Engle WA, McGuire WA, Schreiner RL, Yu PL. Neutrophil storage pool depletion in neonates with sepsis and neutropenia. *J Pediatr*. 1988;113:747–749
19. Koenig JM, Christensen RD. Incidence, neutrophil kinetics, and natural history of neonatal neutropenia associated with maternal hypertension. *N Engl J Med*. 1989;321:557–562
20. Christensen RD. Neutrophil kinetics in the fetus and neonate. *Am J Pediatr Hematol Oncol*. 1989;11:215–223
21. Athens JW, Haab O, Raab S, et al. Leukokinetic studies: the total blood, circulating and marginal granulocyte pools and the granulocyte turnover rate in normal subjects. *J Clin Invest*. 1961;40:989–995
22. Brazy JE, Grimm JK, Little VA. Neonatal manifestations of severe maternal hypertension occurring before the thirty-sixth week of pregnancy. *J Pediatr*. 1982;100:265–271
23. Mouzinho A, Rosenfeld CR, Sanchez PJ, Risser R. Effect of maternal hypertension on neonatal neutropenia and risk of nosocomial infection. *Pediatrics*. 1992;90:430–435
24. Keonig JM, Christensen RD. Neutropenia and thrombocytopenia in infants with Rh hemolytic disease. *J Pediatr*. 1989;114:625–631
25. Schibler K. Leukocyte development and disorders during the neonatal period. In: Christensen RD, ed. *Hematologic Problems of the Neonate*. Philadelphia, PA: WB Saunders Co; 2000:311–342
26. Doran MW, Makhlouf RA, Katz VL, Lawson EE, Stiles AD. Increased incidence of sepsis at birth in neutropenic infants of mothers with pre-eclampsia. *J Pediatr*. 1994;125:452–458
27. Halperin DS, Wacker P, Lacount G, et al. Effects of recombinant human erythropoietin in infants with anemia of prematurity. *J Pediatr*. 1990;116:779–786
28. Shannon KM, Mentzer WC, Abels RI, et al. Recombinant human erythropoietin in the anemia of prematurity: results of a placebo-controlled pilot study. *J Pediatr*. 1991;118:949–955
29. Christensen RD, Koenig JM, Viskochil DH, Rothstein G. Down-modulation of neutrophil production by erythropoietin in human hematopoietic clones. *Blood*. 1989;74:821–826

30. Christensen RD. Hematopoiesis in the fetus and neonate. *Pediatr Res*. 1989;26:531–535
31. Clark SC, Kamen R. The human hematopoietic colony-stimulating factors. *Science*. 1987;236:1229–1237
32. Chen BD, Lin HS, Hsu S. Tumor-promoting phorbol esters inhibit the binding of colony-stimulating factor (CSF-1) to murine peritoneal exudate macrophages. *J Cell Physiol*. 1983;116:207–212
33. Nicola NA, Metcalf D. Binding of the differentiation-inducer, granulocyte-colony-stimulating factor, to responsive but not unresponsive leukemic cell lines. *Proc Natl Acad Sci USA*. 1984;81:3765–3769
34. Nicola NA, Vadas MA, Lopez AF. Down-modulation of receptors for granulocyte colony-stimulating factor on human neutrophils by granulocyte-activating agents. *J Cell Physiol*. 1986;128:501–509
35. Walker F, Nicola NA, Metcalf D, Burgess AW. Hierarchical down-modulation of hematopoietic growth factor receptors. *Cel1*. 1985;43: 269–276
36. Bradley TR, Robinson W, Metcalf D. Colony production in vitro by normal, polycythemic and anaemic bone marrow. *Nature*. 1967;214:511
37. Van Zant G, Goldwasser E. Simultaneous effects of erythropoietin and colony-stimulating factor on bone marrow cells. *Science*. 1977;198: 733–735
38. Hellman S, Grate HE. Haematopoietic stem cells: evidence for competing proliferative demands. *Nature*. 1967;216:65–66
39. Brown MS, Phibbs RH, Garcia JF, Dallman PR. Postnatal changes in erythropoietin levels in untransfused premature infants. *J Pediatr*. 1983; 103:612–617
40. Souza LM, Boone TC, Gabrilove J, et al. Recombinant human granulocyte colony-stimulating factor: effects on normal and leukemic myeloid cells. *Science*. 1986;232:61–65
41. Morstyn G, Campbell L, Souza LM, et al. Effect of granulocyte colony stimulating factor on neutropenia induced by cytotoxic chemotherapy. *Lancet*. 1988;1:667–672
42. Roberts RL, Szelc CM, Scates SM, et al. Neutropenia in an extremely premature infant treated with recombinant human granulocyte colony-stimulating factor. *Am J Dis Child*. 1991;145:808–812
43. Gillan ER, Christensen R, Suen Y, Ellis R, Van de Ven C, Cairo MS. A randomized placebo controlled trial of recombinant human granulocyte colony-stimulating factor administration in newborn infants with presumed sepsis: significant induction of peripheral and bone marrow neutrophilia. *Blood*. 1994;84:1427–1433
44. Russell ARB, Davies EG, Ball SE, Gordon-Smith E. Granulocyte colony-stimulating factor treatment for neonatal neutropenia. *Arch Dis Child*. 1995;72:F53–F54
45. Kocherlakota P, La Gamma EF. Human granulocyte colony-stimulating factor may improve outcome attributable to neonatal sepsis complicated by neutropenia. *Pediatrics*. 1997;100(1). URL: http://www.pediatrics.org/content/full/100/1/e6
46. Kocherlakota P, La Gamma EF. Preliminary report: Rh G-CSF may reduce the incidence of neonatal sepsis in prolonged pre-eclampsia associated neutropenia. *Pediatrics*. 1998;102:1107–1111
47. Makhlouf RA, Doron MW, Bose CL, Price WA, Stiles AD. Administration of granulocyte colony-stimulating factor to neutropenic low birth weight infants of mothers with pre-eclampsia. *J Pediatr*. 1995;126: 454–456
48. La Gamma EF, Alpan O, Kocherlakota P. Effect of granulocyte colony-stimulating factor on pre-eclampsia associated neutropenia. *J Pediatr*. 1995;126:457–459
49. Papile LA, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. *J Pediatr*. 1978;92:529–534.

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