Thrombocytopenia and neutropenia among extremely low birth weight neonates

R.D. Christensen[1]
E. Henry[2]
S.E. Wiedmeier[3]
R.A. Stoddard[4]
M.C. Sola-Visner[5]
D.K. Lambert[1]

[1]Intermountain Healthcare Clinical Research, McKay-Dee Hospital Center, Ogden, UT, [2]the Institute for Health Care Delivery Research, Salt Lake City, UT, [3]LDS Hospital and the Department of Pediatrics, University of Utah College of Medicine Salt Lake City, UT; [4]Utah Valley Regional Medical Center, Provo, UT; [5]the Division of Neonatology, Drexel University College of Medicine and St. Christopher's Hospital for Children, Philadelphia, PA, USA

Correspondence:
Robert D. Christensen, MD, Intermountain Healthcare, 4403 Harrison Blvd, Ogden, UT 84403; USA.
Phone, 801-387-4300
Fax, 801-387-4316
E-mail: rdchris@ihc.com

ABSTRACT

Thrombocytopenia and neutropenia are common in the NICU, and might be over represented among extremely low birth weight neonates (ELBW, ≤1000g birth weight). However, little is known about these issues in the ELBW population, thus we performed cohort analyses of ELBW neonates in a multihospital healthcare system. Seventy-three percent of patients had one or more platelet counts ≤150,000/uL and 80% of these occurred during the first week. Thrombcytopenia was more common in the smallest patients; 85% in those ≤800g, 60% in 801-900g, and 53% in 901-1000g. Platelet transfusions were given to 62%, and >90% of these were for patients who were not bleeding. The mortality rate in those receiving platelet transfusions was twice that of those receiving none (p<0.01). Thirty-eight percent had neutropenia (<1000/uL). It persisted for <24 hrs in 57% and for 1 to 7.5 days in 43%. Most (74%) occurred in the first three days. It was more common among the smallest patients; 63% in those ≤500 g, 44% in 501 to 600 g, and 34% in 801-1000 g. IVIG was given to 28%, and all were given according to guidelines. rG-CSF was given to 13% and 69% were given according to guidelines. Neither the presence of neutropenia nor the severity correlated with mortality rate. Much remains to be discovered about the etiology and best treatments of thrombocytopenia and neutropenia among ELBW neonates.

Thrombocytopenia and neutropenia are common in the neonatal intensive care unit (NICU). Previous reports estimate that 18 to 35% of patients admitted to a NICU will have one or more platelet counts ≤150,000/uL[1-5] and 8% will have one or more neutrophil counts <1000/uL[6,7] at some time before discharge. To better understand thrombocytopenia and neutropenia in the ELBW population, we performed an historic cohort analysis of neonates cared for in the four Intermountain Healthcare (IHC) NICUs. From archived electronic records and from paper chart analysis we accessed all platelet counts and all neutrophil counts obtained on these patients. When a platelet count ≤150,000/uL or a neutrophil count <1000/uL was identified, we determined the day of life this was first recognized, the duration of the cytopenia, the tests used to discover the underlying causes, the underlying causes that were ascribed, the use of platelet transfusions, IVIG, and rG-CSF, and the mortality rates.

Methods

Data were collected as deidentified limited data sets from archived IHC records. The information collected was limited to the complete blood counts and the information displayed in tables and figures of this report. Data were obtained for patients admitted to the NICU at McKay-Dee Hospital, Ogden, UT, LDS Hospital, Salt Lake City, UT, Primary Children's Medical Center, Salt Lake City, UT, and Utah Valley Regional Medical Center, Provo, UT, USA. For the thrombocytopenia study, patients were included if they had a date of birth from January 1, 2003 through December 31, 2004, and with a birth weight of ≤1000g. For the neutropenia study patients were included if they had a data of birth from July 1, 2002 through June 30, 2005. The IHC Institutional Review Board approved the study.

Descriptive statistics were calculated using Statit (Corvallis, OR). Means and standard deviations were used to express values in groups that were normally distributed, and medians and ranges to express values in groups that were not. Differences in categorical variables were assessed using the χ^2 test. A Student t test was used to assess continuous variables. Statistical significance was set as $p < 0.05$. All hypotheses were two-tailed.

Results

The thrombocytopenia study consisted of 284 ELBW infants and the neutropenia study consisted of 338. The number of platelet counts obtained per patient ranged from 4 to 411 (median, 24) and the number of neutrophil counts obtained per patient ranged from 1 to 123 (median, 16). The overall incidence of thrombocytopenia was 73% and of neutropenia was 38%.

Thrombocytopenia

The birth weight was lower among the 208 who developed thrombocytopenia (720±150 grams, mean±SD) than among the 76 who did not (808+142 grams, $p<0.001$). The gestational age at delivery was similar between those who developed thrombocytopenia (26.1±2.2 wks) and those who did not (26.4±2.0 wks, $p = 0.24$). No differences were observed in gender, mode of delivery, five-minute Apgar scores, or race or ethnicity, between those who did vs. did not develop thrombocytopenia.

In 58% of the thrombocytopenic ELBW neonates, the thrombocytopenia was detected in the first three days after birth (Figure 1). Only 20% of those who developed thrombocytopenia had this first recognized after the first week of life. Six cases (3%) were not detected until seven weeks or more.

Thrombocytopenia was more common in the lowest birth weight groups (Figure 2). It was found in 85% of those weighing ≤800g at birth, in 60% of those 801-900 g, and in 53% of those 901-1000g. The duration of thrombocytopenia ranged from less than one day to 50 days. Twenty-one of the 208 (10%) had either very transient thrombocytopenia, or had an erroneously low platelet count, because a repeat count performed within 24 hours was normal without an intervening platelet transfusion.

The lowest recorded platelet count was <20,000/uL in 9% of the thrombocytopenic patients; it was ≤50,000/uL in 38% of the thrombocytopenic patients, and it was ≤100,000/uL in 77%. The remaining 23% had mild thrombocytopenia, with the lowest count between 101,000 and 149,000/uL. The mortality rate did not correlate with the lowest recorded platelet count. Among those with the most severe thrombocytopenia (<20,000/uL) 16.7% died, among those with a lowest count in the range of 20-50,000/uL 16.4% died, among those with a lowest count in the range of 51-100,000/uL 19.7% died, and among those with a lowest count in the range of 101-149,000/uL 14.6% died.

The mortality rates among ELBW neonates who did vs. did not receive platelet transfusions are shown in Table 1. Seventy-five neonates had no thrombocytopenia and no platelet transfusions. Seventy-nine others had thrombocytopenia but no platelet transfusions. One patient (not listed in the table) had a platelet transfu-
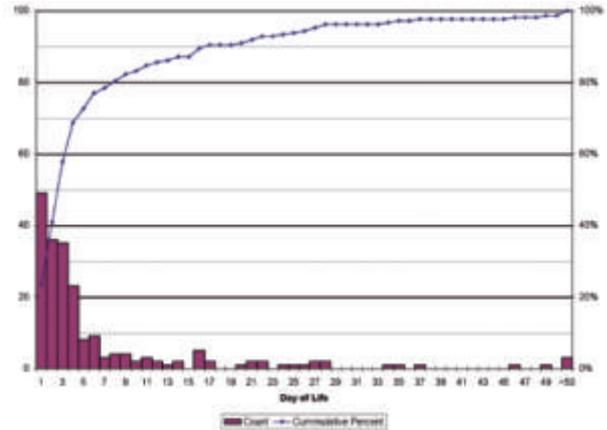

Figure 1. The day of life thrombocytopenia was recognized. The figure shows the day of life thrombocytopenia was detected among 208 ELBW neonates.
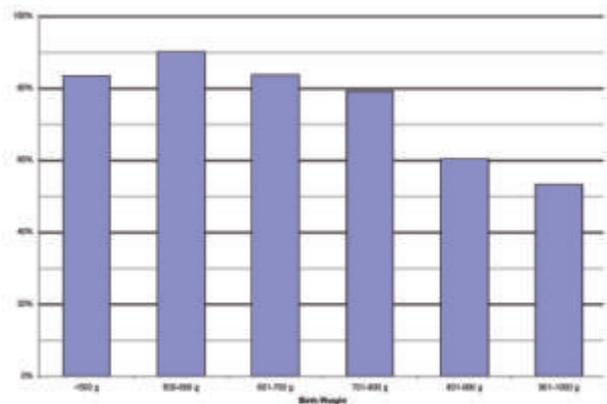

Figure 2. Thrombocytopenia as related to birth weight. The incidence of thrombocytopenia among 284 ELBW neonates, as related to birth weight.

sion but was not thrombocytopenic. Thus, 154 ELBW neonates received no platelet transfusions; the mortality rate in this group was 12%. One-hundred-twenty-nine were thrombocytopenic and received one or more platelet transfusions (range, 1 to 51 transfusions/patient). The mortality rate in this group was 23% ($p<0.01$ vs. those who received no platelet transfusions, Table 2). Most of the patients who developed thrombocytopenia and died, did so while their platelet count was still low (Table 1).

The platelet counts that preceded 356 platelet transfusions are shown in Table 2. For patients who had multiple platelet transfusions, information was collected only for their first five platelet transfusions. The minor-

Table 1. Platelet transfusions and mortality. The number of platelet transfusions administered and the mortality rates are shown for 284 ELBW neonates.

	Mortality % (number)	Death occurred after the thrombocytopenia resolved	Death occurred while thrombocytopenia was still a problem
No thrombocytopenia and no pl transfusions	15% (11/75)	-	-
Thrombocytopenia but no platelet transfusions	9% (7/79)	1	6
Thrombocytopenia and 1-5 platelet transfusions	20% (19/95)	1	18
Thrombocytopenia and >5 platelet transfusions	29% (10/34)	2	8

Table 2. Platelet transfusion antecedents. Whether or not the patient had active bleeding when a platelet transfusion was ordered, and the platelet count at which a platelet transfusion was ordered, are shown for ELBW neonates who received one or more platelet transfusions. Information is given for 356 transfusions.

	Platelet Transfusions				
	First	Second	Third	Fourth	Fifth
Number (n) transfusions	N=126	N=85	N=65	N=43	N=37
Active bleeding*, pl >150,000/uL	0	1	0	0	0
Active bleeding*, pl 100,000-149,000/uL	4	2	2	0	1
Active bleeding*, pl <100,000/uL	9	3	0	1	2
Active bleeding*, pl unknown	1	1	1	1	0
Not bleeding, pl >150,000/uL	1	0	0	0	0
Not bleeding, pl 100,000-149,000/uL	8	10	3	4	1
Not bleeding, pl 50,000-99,000/uL	73	49	43	16	18
Not bleeding, pl 20,000-49,000/uL	27	17	13	19	14
Not bleeding, pl <20,000/uL	3	1	2	2	1
Not bleeding, pl unknown	0	1	1	0	0

ity of platelet transfusions (8%) were ordered for patients with clinical hemorrhage; most were ordered when no record of clinical hemorrhage was found among the physician or nursing notes. The majority (61%) of these latter prophylactic platelet transfusions were ordered when the platelet count was between 50,000 and 99,000/uL. Twenty-eight percent of the prophylactic transfusions were ordered when the platelet count was in the range of 20,000 to 49,000/uL, and only 2.8% of the platelet transfusions were ordered when the platelet count was <20,000/uL.

Fifty-six percent of the thrombocytopenic neonates had a bacterial culture performed to evaluate the underlying cause of the thrombocytopenia. Forty-nine percent had a DIC screen performed, 10% had CMV cultures performed, 3% had lineograms or other imaging studies in an attempt to detect thrombi, and 2% had chromosomes or other genetic testing as part of the search for an etiology of the thrombocytopenia. Two % had viral cultures or viral titers drawn and <1% had anti-platelet antibody testing performed.

The explanations given for the thrombocytopenia are shown in Table 3. Almost half had no explanation discovered. The most commonly applied explanation for thrombocytopenia was that the patient was SGA or was delivered after PIH. None had a diagnosis made of neonatal alloimmune thrombocytopenia, maternal autoimmune thrombocytopenia, viral infection, or drug-associated thrombocytopenia.

Neutropenia

Demographic features of the ELBW neonates with neutropenia vs. those who did not develop neutropenia, are shown in Table 4. In 53% of the neutropenic neonates, the neutropenia was detected on the first day of life (Figure 3), and in 74% it was detected by day three. Only 22% of those who developed neutropenia did so after the first week of life. Nine cases (7%) were not detected until seven weeks or more.

Neutropenia was slightly more common at the lowest birth weights (Figure 4). It was found in 63% of those weighing <500 g at birth, 44% of those weighing 501 to 600 g, and in 34% of those weighing 801g

Table 3. Contributing factors, used to explain the thrombocytopenia. The likely underlying causes, explaining the presence of thrombocytopenia among 208 ELBW neonates, are shown. In some instances, more than one contributing factor was ascribed (for instance, both bacterial sepsis and DIC). Therefore, the sum of each column exceeds 100%.

Factors identified to explain the thrombocytopenia	Number of patients with thrombocytopenia (n=208) who had this as the likely underlying explanation	Patients with thrombocytopenia first recognized in the first three days, (n=120) who had this as the likely underlying explanation	Patients with thrombocytopenia first recognized after day three (n=88) who had this as the likely underlying explanation
Unexplained or undiagnosed	101	50	51
SGA or PIH	76	55	21
DIC	40	32	8
Bacterial infection	36	23	13
Fungal Infection	12	7	5
NEC	11	1	10
Genetic	2*	2	0
Thrombus	1**	0	1
Drug Associated	0	0	0
Alloimmune	0	0	0
Autoimmune	0	0	0
CMV	0	0	0
Non-CMV viral infection	0	0	0

*One trisomy 18 and one TAR syndrome; ** Right atrial thrombus associated with a peripherally inserted central venous catheter
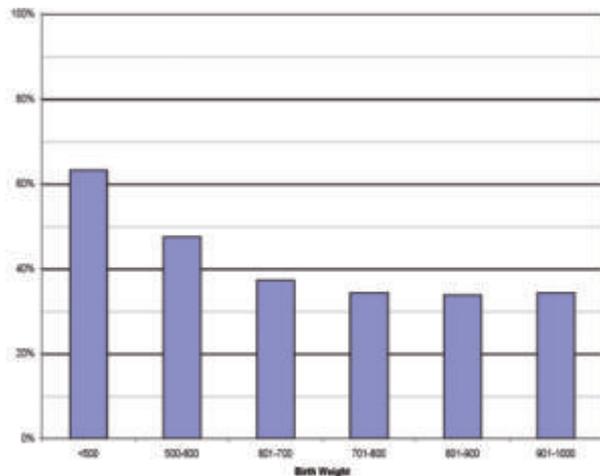

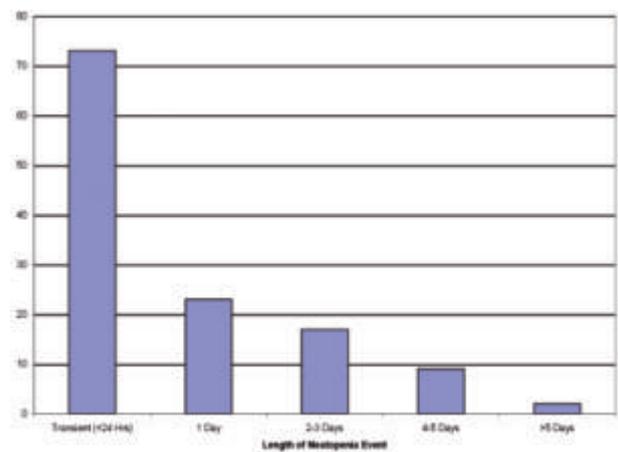**Figure 4. Incidence of neutropenia, among ELBW neonates, according to birth weight.**

Figure 5. Duration of neutropenia (days) in 128 ELBW neonates.

or more.

The duration of neutropenia ranged from less than one day to just over seven days (figure 5). Fifty-seven percent (73/128) had transient neutropenia, because a repeat count performed within 24 hours was >1000/uL, but 43% continued to have neutropenia for more than one day. The longest duration observed was 7.5 days.

The lowest neutrophil count recorded, among each of the neutropenic patients, is shown in Figure 6. In just under half (48%) of the cases the lowest recorded count was ≤500/uL. In 21% the lowest recorded count was in the range of 800 to 1000/uL.

The presence of neutropenia did not correlate with mortality rate; neither did the severity (lowest recorded count) of the neutropenia, or its duration (days), correlate with mortality rate. For instance, the mortality rate among those with a lowest recorded count of ≤500/uL (8/45 died 17.8%) was not significantly higher than among those with a lowest recorded count >750/uL (3/27 died 11.1%, p=0.27). However, the highest morality rate group was those with early-onset bacterial sepsis and neutropenia, where four of six died.

Most of the neutropenic ELBW neonates did not have either IVIG or rG-CSF administered. When IVIG was used, it was ordered in accordance with our published guidelines 100% of the time.[8] When rG-CSF was used, it was

Table 4. Demographic Features. Features of 338 ELBW neonates who, during their hospital stay, had no neutropenia detected, vs. had early-onset neutropenia (detected in the first three days of life), or late-onset neutropenia (detected after the first three days of life), or early-onset neutropenia that resolved followed by one or more episodes of late-onset neutropenia.

	No neutropenia N=210	Early-onset neutropenia only * N=70	Late-onset neutropenia only** N=33	Both early-onset and late-onset neutropenia*** N=25
Birth Weight (grams±SD)	772 ±148	723±173	785±132	691 ±157
Gender (% male)	51%	56%	55%	44%
Gestational Age at Delivery (wks) (Median)	26	26	26	26
Mode of Delivery (% vaginal)	29%	10%	36%	8%
Five-Minute Apgar Score <6 (%)	29%	28%	19%	23%
SGA (%)	17%	37%	12%	28%
PIH (%)	9%	39%	15%	60%
Race/Ethnicity (% White)	74%	72%	71%	67%

*Early-onset neutropenia was defined as a blood neutrophil concentration <1000/uL during the first three days of life. Patients listed in this column had early-onset neutropenia, but they did not subsequently develop late-onset neutropenia. **Late-onset neutropenia was defined as a blood neutrophil concentration <1000/uL, detected after the first three days of life. Patients listed in this column had a normal neutrophil concentration during the first three days of life, but developed neutropenia sometime between four days of age and hospital discharge. ***Patients listed in this column had early-onset neutropenia that resolved, and then subsequently developed one or more episodes of late-onset neutropenia. g; gram. SGA; small for gestational age, weight <10% for gestational age. PIH; mother had pregnancy-induced hypertension.

Table 5. IVIG and rG-CSF usage among 128 ELBW neonates with 153 episodes of neutropenia.

	IVIG administered	IVIG used according to guidelines*	rG-CSF administered	rG-CSF used according to guidelines**
Neutropenia during the first 3 days (n=95)	25/95 (26%)	25/25	15/95 (16%)	10/15
Neutropenia after the first 3 days (n=58)	11/58 (19%)	11/11	1/58 (2%)	1/1

*Guidelines for using IVIG = ANC <1000/uL, bacterial infection proven or highly likely, hypotension, and significant clinical deterioration. Dose = 750 mg/kg (6).
**Guidelines for using rG-CSF = Known to be a case of severe congenital neutropenia, or ANC <500/uL for two days or more, or ANC <1000/uL for five days or more. Dose = 10 lg/k/day for three days (6).
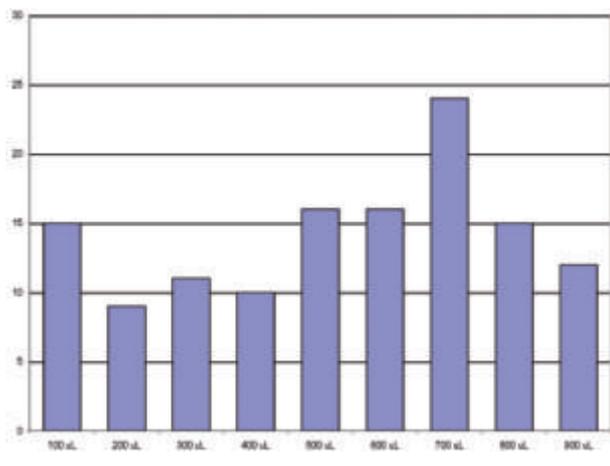

Figure 6. Severity of the neutropenia. The lowest blood neutrophil concentration recorded is shown for 128 ELBW neonates with neutropenia.

ordered in accordance with our guidelines 69% of the time.[8]

The likely explanations discovered as underlying antecedents, or causes of the neutropenia, are shown in Table 5. The majority of the cases detected in the first three days after birth were associated with SGA or PIH. The majority of the cases detected after the first three days were associated with NEC or nosocomial infection. Over 1/3 of the cases had no apparent explanation for the neutropenia or were incompletely evaluated. None of the neutropenic patients had studies done to assess the presence of alloimmune or autoimmune neutropenia. None of the patients had neutropenia that persisted beyond 7.5 days.

Discussion

Thrombocytopenia and neutropenia are rare in a well baby nursery,[9,10] but in a NICU these are relatively common, 18 to 35% reported to have thrombocytopenia and 8% reported to have neutropenia at some time during the NICU stay.[1-7] On the basis of our experience, we speculated that ELBW neonates have a yet higher incidence of thrombocytopenia and or neutropenia. Indeed, in the present study we observed that 73% of ELBW neonates had thrombocytopenia and 38% had neutropenia.

Thrombocytopenia and neutropenia can have origins

Table 6. Contributing factors, used to explain the neutropenia. The likely underlying causes explaining the presence of 153 episodes of neutropenia among 128 ELBW neonates are shown. Ninety-five episodes occurred in the first three days of life and 58 after the first three days. In some instances, more than one contributing factor was ascribed. Therefore, the sum of each column exceeds 100%.

Factor identified to explain the neutropenia	Episodes of neutropenia in the first 3 days of life where this was the likely underlying explanation (n=95)	Episodes of neutropenia after the first 3 days of life where this was the likely underlying explanation (n=58)
SGA or PIH	65 (68%)	5 (9%)
Unexplained, Undiagnosed, or Idiopathic	20 (21%)	25 (43%)
Bacterial infection	6 (6%)	11 (19%)
NEC	1 (1%)	18 (31%)
Twin-twin transfusion	6 (6%)	1 (2%)
Fungal sepsis	0	3 (5%)**
Genetic or metabolic abnormality	1 (1%)*	0
Drug associated	0	3 (5%)**
Alloimmune	0	0
Autoimmune	0	0
Viral infection	0	1 (2%)***

*TAR syndrome. The neutropenia spontaneously resolved after three days, without IVIG or rG-CSF treatment. ** All three patients were receiving amphotericin. It was not clear whether the neutropenia should be ascribed to the fungal sepsis or the amphotericin. In each case, the neutropenia developed at least two days after the onset of treatment with amphotericin. *** Cutaneous herpes simplex.

either before or after birth. Due to the retrospective nature of this study, it was not possible to know how many of these had prenatal cytopenia. Furthermore there was no pre-specified list of tests to be performed in order to assess the underlying causes of the cytopenia or measure its duration. However, we speculate that the majority of cases were either of prenatal onset or due to factors arising within the first days after birth. We base this on the finding that most cases were recognized on the first day of life, and only about 20% were identified after the first week.

We observed that about half of the cases of thrombocytopenia or neutropenia had no explanation recognized. In otherwise well-appearing term babies with thrombocytopenia, the diagnosis is likely to be neonatal alloimmune thrombocytopenia or due to maternal autoimmune disease,[11,12] but we found no documented cases of either of these varieties. Similarly, alloimmune neutropenia is a relatively common condition among neutropenic term neonates, but we observed no cases among these ELBW neonates. We speculate that the lack of immune-mediated cases was the result of inadequate testing in this population.

Platelet transfusions are recommended for neonates who have low platelet counts and clinical bleeding.[16] They are also recommended as prophylaxis against bleeding if the count falls sufficiently low.[3,16] Precisely how low to permit a platelet count to fall in an ELBW neonate before ordering a platelet transfusion is not known. We found that platelet transfusions were nearly always given for prophylaxis against bleeding rather than to treat active bleeding. We identified no consistent criteria for ordering prophylactic platelet transfu-

sions, but we found that those given platelet transfusions had a mortality rate twice that of those who receive no platelet transfusions. We speculate that this increase in mortality rate is related to the underlying illnesses of those who received platelet transfusions, as opposed to being due to a toxic effect of the transfusions.

We found that 43% of the cases of late-onset neutropenia had no recognized underlying cause. Some of these may have been due to the benign variety of neutropenia sometimes termed, *idiopathic neutropenia of prematurity*.[17-20] That variety probably does not constitute a significant host-defense deficiency, because patients generally maintain a bone marrow neutrophil reserve that can be mobilized as needed to contend with bacteria.[20]

IVIG administration has sometimes been advocated for septic, neutropenic, neonates, with the hope of providing opsonic antibody against infecting organisms, but its use has not been well defined.[21] In a recent Cochrane Review of this usage of IVIG, Olson and Lacy concluded that the available data suggest a benefit in reducing morality.[21] In a consensus development process we suggested that the use of IVIG was reasonable in neonates who had a blood neutrophil count <1000/uL and proven or very likely bacterial sepsis and shock syndrome.[22] In the present study we observed that IVIG was used in accordance with this recommendation. However, it is unclear how much benefit the patients derived from this practice.

rG-CSF has been approved for use among patients with severe chronic neutropenia. Although controversial, rG-CSF has generally not been regarded as useful

in treating neonates with sepsis and neutropenia.[22–27] A Cochrane Review of this usage of rG-CSF concludes that while more study is needed, the available data suggest that it has no benefit in reducing morality.[27] In a consensus development process, we suggested that rG-CSF should not be routinely used to treat neonates who have sepsis and neutropenia, but that it should be reserved for neonates who may indeed have a variety of severe chronic neutropenia, whose neutrophil counts are <500/uL for two days or more, or <1000/uL for five days or more.[8] In the present study we observed that when rG-CSF was used in neutropenic ELBW neonates, it was given in accordance with this recommendation in 69% of the cases. As with IVIG usage among neutropenic ELBW neonates, it is unclear from this study how much benefit these patients derived from rG-CSF administration.

In general, we found neutropenia in ELBW neonates to be transient, generally lasting only one day, and rarely more than three. We failed to find an association between neutropenia and mortality, except in the circumstance of proven early-onset bacterial infection where it was associated with a poor outcome. On this basis, we judge that neutropenia among ELBW is generally not a significant host-defense defect, and (except when it accompanies early-onset sepsis) likely needs no specific treatment. For ELBW neonates with early-onset sepsis, neutropenia, and shock syndrome, IVIG administration is based on biologically plausible rationale, but its efficacy requires further study.

Since so many of the cases we reviewed were of idiopathic causation, or were incompletely evaluated, we judge that a more consistent approach is needed for evaluating thrombocytopenia and neutropenia in this group of patients. We also judge that additional work is needed to define which cases are truly innocuous and which are likely to benefit from various treatments.

References

1. Mehta P, Vasa R, Neumann L, Karpatkin, M. Thrombocytopenia in the high-risk infant. J Pediatr 1980; 97: 791-794.
2. Castle V, Andrew M, Kelton J, Giron D, Johnston M, Carter C. Frequency and mechanism of neonatal thrombocytopenia. J Pediatr 1986;108: 749-755.
3. Roberts IA, Murray NA. Thrombocytopenia in the newborn. Curr Opin Pediatr 2003; 15: 17-23.
4. Sola MC. Evaluation and treatment of severe and prolonged thrombocytopenia in neonates. Clin Perinatol 2004: 31; 1-14.
5. Aman I, Hassan KA, Ahmad TM. The study of thrombocytopenia in sick neonates. J Coll Physicians Surg Pak 2004; 14: 282-285.
6. Christensen RD, Calhoun DA, Rimsza LM. A practical approach to evaluating and treating neutropenia in the neonatal intensive care unit. Clin Perinatol 2000;27:577-601.
7. Funke A, Berner R, Traichel B, Schmeisser D, Leititis JU, Niemeyer CM. Frequency, natural course, and outcome of neonatal neutropenia. Pediatrics. 2000;106:45-51.
8. Calhoun DA, Calhoun DA, Christensen RD, Edstrom CS, Juul SE, Ohls RK, Schibler KR, Sola MC, Sullivan SE. Consistent approaches to procedures and practices in neonatal hematology. Clin Perinatol 2000;27:733-753.
9. Dreyfus M, Kaplan C, Verdy E, Schlegel N, Durand-Zaleski I, Tchernia G. Frequency of immune thrombocytopenia in newborns: a prospective study. Immune Thrombocytopenia Working Group. Blood 1997; 15; 89:4402-4406.
10. McPherson RJ, Juul S. Patterns of thrombocytosis and thrombocytopenia in hospitalized neonates. J Perinatol 2005; 215: 166-172.
11. Blanchette VS, Peters MA, Pegg-Feige K. Alloimmune thrombocytopenia. Review from a neonatal intensive care unit. Curr Stud Hematol Blood Transfus 1986; 52: 87-96.
12. Bussel, J. Alloimmune thrombocytopenia in the fetus and newborn. Semin Thromb Hemost 2001; 27: 245-252.
13. Boxer LA. Immune neutropenias. Clinical and biological implications. Am J Pediatr Hematol Oncol. 1981;3:89-96.
14. Maheshwari A, Christensen RD, Calhoun DA. Immune-mediated neutropenia in the neonate. Acta Paediatr Suppl 2002;91:98-103.
15. Bussel J, Lalezari P, Fikrig S. Intravenous treatment with gamma-globulin of autoimmune neutropenia of infancy. J Pediatr 1988;112:298-301.
16. Sola MC, Del Vecchio A, Rimsza LM. Evaluation and treatment of thrombocytopenia in the neonatal intensive care unit. Clin Perinatol 2000; 27: 655-660.
17. Koenig JM and Christensen RD. Incidence, neutrophil kinetics, and natural history of neonatal neutropenia associated with maternal hypertension. N Engl J Med. 1989;321:557-562.
18. Chirico G, Motta M, Villani P, Cavazza A, Cardone ML. Late-onset neutropenia in very low birthweight infants. Acta Paediatr Suppl 2002;91:104-108.
19. Omar SA, Salhadar A, Wooliever DE, Alsgaard PK. Late-onset neutropenia in very low birth weight infants. Pediatrics 2000;106:E55.
20. Gonzalez BE, Mercado CK, Johnson L, Brodsky NL, Bhandari V. Early markers of late-onset sepsis in premature neonates: clinical, hematological and cytokine profile. J Perinat Med 2003;31:60-68.
21. Juul SE, Calhoun DA, Christensen RD. "Idiopathic neutropenia" in very low birthweight infants. Acta Paediatr. 1998;87:963-968.
22. Juul SE, Christensen RD. Effect of recombinant granulocyte colony-stimulating factor on blood neutrophil concentrations among patients with "idiopathic neonatal neutropenia": a randomized, placebo-controlled trial. J Perinatol 2003;23:493-497.
23. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Cochrane Database Syst Rev 2004;1:CD001239.
24. Schibler KR, Osborne KA, Leung LY, Le TV, Baker SI, Thompson DD. A randomized, placebo-controlled trial of granulocyte colony-stimulating factor administration to newborn infants with neutropenia and clinical signs of early-onset sepsis. Pediatrics. 1998;102:6-13.
25. Bedford Russell AR, Emmerson AJ, Wilkinson N, Chant T, Sweet DG, Halliday HL, Holland B, Davies EG. A trial of recombinant human granulocyte colony stimulating factor for the treatment of very low birthweight infants with presumed sepsis and neutropenia. Arch Dis Child Fetal Neonatal Ed. 2001;84:F172-176.
26. Bilgin K, Yaramis A, Haspolat K, Tas MA, Gunbey S, Derman O. A randomized trial of granulocyte-macrophage colony-stimulating factor in neonates with sepsis and neutropenia. Pediatrics 2001;107:36-41.
27. Miura E, Procianoy RS, Bittar C, Miura CS, Miura MS, Mello C, Christensen RD. A randomized, double-masked, placebo-controlled trial of recombinant granulocyte colony-stimulating factor administration to preterm infants with the clinical diagnosis of early-onset sepsis. Pediatrics. 2001;107:30-35.
28. Calhoun DA, Lunoe M, Du Y, Hutson AD, Veerman M, Christensen RD. Granulocyte colony-stimulating factor serum and urine concentrations in neutropenic neonates before and after intravenous administration of recombinant granulocyte colony-stimulating factor. Pediatrics. 2000;105:392-397.
29. Carr R, Modi N, Dore C. G-CSF and GM-CSF for treating or preventing neonatal infections. Cochrane Database Syst Rev 2003;3: CD003066.