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Association of BPD and IVH with early neutrophil and white counts in VLBW neonates with gestational age <32 weeks

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Abstract

Objectives—To investigate associations between early low neutrophil count from routine blood samples, white blood count (WBC), pregnancy complications and neonatal outcomes for very low birth weight infants (VLBW ≤1500g) with gestational age <32 weeks.

Patients and Methods—Information was abstracted on all infants admitted to level III NICUs in Wisconsin 2003-2004. 1002 (78%) had differential and corrected total white counts within 2 ½ hours of birth. Data analyses included frequency tables, binary logistic, ordinal logistc and ordinary regression.

Results—Low neutrophil count (<1000/μL) was strongly associated with low WBC, pregnancy complications and antenatal steroids. Low neutrophil count predicted bronchopulmonary dysplasia severity level (BPD) (OR: 1.7, 95% CI: 1.1-2.7) and intraventricular hemorrhage (IVH) grade (OR: 2.2, 95% CI: 1.3-3.8).

Conclusions—Early neutrophil counts may have multiple causes interfering with their routine use as an inflammatory marker. Nonetheless, low neutrophil count has consistent independent associations with outcomes.

Keywords

WBC; BPD; IVH; SNAP-II; NICU; risk factors

INTRODUCTION

Experimental studies of lambs and monkeys as well as careful observational studies of selected very low birth weight (VLBW, ≤1500g) human neonates, have shown that a low number of circulating neutrophils in peripheral blood shortly after birth can be a marker for inflammatory processes and a predictor of neonatal lung disease (1-4), including bronchopulmonary dysplasia (4). There are also indications that a low number of neutrophils may be predictive of other neonatal complications (4). The previous human study (4) excluded neonates born following certain maternal complications and treatments such as pregnancy-induced hypertension and antenatal steroid therapy that are associated with inhibition or enhancement of neutrophil counts, (5-9). These exclusions limit the applicability of the findings, especially since antenatal steroid therapy is now almost ubiquitous. In addition, the neutrophil count in the above studies was mapped by sampling cord and/or early blood in well controlled or single

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hospital settings. It is therefore not clear whether information from routine differential white counts obtained on an unselected population of VLBW NICU admissions carry predictive value for future complications and outcomes.

The Newborn Lung project has assembled a database with extensive clinical information on all VLBW infants born and admitted to NICUs in Wisconsin during the entire calendar years 2003 and 2004, thus providing a large unselected cohort of VLBW infants experiencing a range of regular care. We analyze neutrophil counts in routine blood samples taken within two and a half hours of birth for the subgroup born at less than 32 weeks gestation. We hypothesized that: (1) both neutrophil and total white blood counts are associated with pregnancy complications and neonatal characteristics. (2) Neutrophil count, but not total white count is associated with early disease severity, bronchopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH).

PATIENTS AND METHODS

All VLBW neonates born in the years 2003 and 2004 and admitted to all 16 level III NICUs in Wisconsin, and Wisconsin residents admitted to 1 NICU located in Minnesota near the Wisconsin border were eligible to participate in the parent study (the Newborn Lung Project). A total of 1479 neonates had de-identified clinical abstract data submitted to the study. This number closely matches the number of VLBW births in Wisconsin reported to the vital statistics division of the state minus delivery room deaths. As both BPD and IVH were exceedingly rare in neonates born at 32 weeks or greater gestational age, the current paper targets the subgroup of 1283 VLBW neonates born at less than 32 weeks gestation. Institutional Review Boards at the University of Wisconsin and at all participating hospitals approved the study protocol.

Data were abstracted by NICU nurses, who were trained in study procedures, at each of the hospitals, according to detailed guidelines. One thousand two neonates (78% of those with gestational age less than 32 weeks) were found to have records of differential white counts, adjusted for nucleated red cells, performed within 2.5 hours of birth, and are included in this report. Information on the time of sample, total white count and the percentage of mature neutrophils was abstracted. Other infant variables abstracted and used in the current analysis were birth weight, gestational age, assessment of small for gestational age (SGA), diagnosis of sepsis and variables needed for computing the SNAP-II score of baseline physiology (10). The SNAP-II score is based on 6 indicators resulting in a score with maximum possible range 0-115 where a higher score indicates worse generic baseline physiologic status. Information was abstracted on ultrasound diagnosis of IVH at any time during the NICU stay. Hospitals graded IVH severity by the method of Papile (11) into grades 0-4, where 0 designates no IVH. BPD was graded according to the NIH criteria (12) based on use and level of supplemental oxygen at 36 weeks postmenstrual age (PMA), as at least “moderate BPD” (level 2 and above) and “severe BPD” (level 3). Level 2 corresponds to the often used diagnostic criterion for BPD of any oxygen use at 36 weeks PMA. Presence and day of life of culture confirmed sepsis during the NICU stay were recorded. We considered as outcomes, sepsis diagnosed on the day of birth or following day, as well as sepsis during the NICU stay.

Information was also abstracted on the mother including pregnancy induced hypertension, pathological diagnosis and/or clinical signs of amnionitis or chorioamnionitis (13), method and duration of rupture of membranes, and administration of antenatal steroids. Spontaneous rupture of membranes of duration greater than 24 hours was considered prolonged rupture of membranes (PROM).

Statistical analyses were performed in SAS version 9.1.3 (14). Descriptive statistics are presented as mean (sd) for birth weight, gestational age and SNAP II score and as percentage

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falling in indicated categories for all other variables. WBC and neutrophil counts were categorized according to quartiles rounded to the nearest 1000/ μL. Variables were compared across white count and neutrophil count quartiles by chi-square tests for general association for binary and dichotomized variables and analysis of variance for continuous variables. Asterisks in Tables 1 and 2 indicate the significance of these comparisons. For comparison with other studies (15) the percentage with low neutrophil count is separately tabulated by white count quartiles for infants born at extremely low birth weight (< 1000g). Neutrophil count in the lowest quartile (<1000/ μL.) was considered "low". This cut point is close to that previously used in several studies (9,16) to define neutropenia. Logistic regression was used to identify pregnancy related factors and birth characteristics associated with low neutrophil count. Due to the strong association of WBC with neutrophil count, WBC categories were adjusted for in all models. Logistic regression was used to examine whether the percentages with BPD, IVH and sepsis were associated with neutrophil count. Associations were quantified as odds ratios (OR) with 95% confidence intervals (CI). These analyses were performed with BPD and IVH dichotomized by severity cut-points as separate binary outcomes, and also with the BPD levels and IVH grades as ordinal outcomes. A statistical test for the proportional odds assumption (14) was used to assess what severity levels could be combined into the ordinal regression. Ordinary regression was used to examine whether mean SNAP II score differed by neutrophil count categories. The associations of low neutrophil count with SNAP II were quantified as differences with 95% confidence intervals (CI). Asterisks in Table 3 indicate statistical significance of odds ratios and differences. All interactions were tested in all models to determine whether odds ratios and differences between those with low and not low neutrophil levels differed between subgroups of neonates. Associations and interactions were considered statistically significant at $p<0.05$.

RESULTS

In the target group of VLBW neonates with gestational age <32 weeks, those who did not have corrected differential white counts within 2.5 hours of birth available, differed from those who did only by a marginally lower Apgar score, and had similar mean birth weight, gestational age and baseline physiology. The percentage with white blood count information available did vary significantly between hospitals ($p<0.001$) ranging from 44% to 94%.

Table 1 contains descriptive statistics on the group overall and comparisons by white blood cell count categories formed by quartiles of the distribution rounded to the nearest 1000. Infant characteristics such as birth weight, gestational age, and the percent SGA differed statistically significantly and substantively between white blood count (WBC) quartiles. Pregnancy complications also differed considerably, with pregnancy induced hypertension being much more common among mothers of the infants in the lowest WBC quartiles, and PROM being much more common in the highest. Consistent with this finding, there were also more infants with mothers who had amnionitis/ chorioamnionitis in the higher WBC quartiles. The percentage of infants with low neutrophil counts (i.e. in the lowest quartile of <1000/ μL) differed between WBC quartiles. Only 1 infant with WBC over 12000/μL had low neutrophil count.

The subgroup of infants who were born extremely low birth weight, had significantly lower neutrophil counts than those who were larger ($p=0.024$). The percentage with low neutrophil count among ELBW neonates also differed across WBC categories (Table 1).

Table 2 shows a comparison based on neutrophil quartiles rounded to the nearest 1000/ μL. A picture similar to that seen in Table 1 emerges. However, in contrast to the situation for WBC, the neutrophil quartiles were significantly associated with the mother having received antenatal

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steroids, and with sepsis, BPD and IVH outcomes for the infant. The largest differences in outcomes tended to occur between the lowest neutrophil quartile and the three higher quartiles.

Multiple logistic regression analysis showed that, once WBC categories were taken into account, pregnancy complications and being born SGA lost statistical significance in predicting neutrophil count. Neutrophil count <1000/μL remained associated with birth weight (OR= 0.87 with 95% CI: 0.81-0.93 per 100g higher), male sex (OR=1.6 with 95% CI: 1.1-2.3) and the mother receiving antenatal steroids (OR=0.51 with 95% CI:0.33-0.81).

Analyses of association of low neutrophil count with SNAP-II, BPD and IVH shown in Table 3, exclude the highest WBC quartile, as low neutrophil count was virtually absent among these infants. However, the overall results were affected very little by this exclusion. Analyses shown in Table 3 were performed by WBC quartile as well as overall, adjusting for the WBC categories shown. Results are also shown additionally adjusted for the significant predictors of low neutrophil count from above, birth weight, sex, and antenatal steroids as well as for sepsis during the NICU stay. The adjusted models also included gestational age as a predictor due to its importance in predicting infant outcomes.

It is seen in Table 3 that SNAP-II, BPD and IVH grades 2 and above were generally predicted by low neutrophil count. IVH including grade 1 and above was not predicted by low neutrophil count. The odds ratios are low for BPD and moderate for IVH. All levels were included in the ordinal regression of BPD in Table 3. However, statistical testing indicated that the association of grade 1 IVH with neutrophil count differed from that of more severe IVH grades ($p<0.0001$). Grade 1 was therefore not included in the ordinal regressions of IVH grades shown in the last two rows of Table 3, which reflect associations across IVH grades 2 and above. For all outcomes, the associations with low neutrophil count appear strongest when the WBC falls between 5000/μL and 7000/μL. In fact, all odds ratios for IVH grade 2 and above and the SNAP-II difference were statistically significant and strong within the WBC 5000-7000//μL category. However, formal tests for interaction indicated that the magnitude of association between low neutrophil count and outcomes, as expressed by odds ratios and SNAP-II differences in Table 3, did not differ statistically significantly between WBC categories. It may be noted that adjusting for sepsis did not much alter the estimated odds ratios. Sepsis itself was associated with BPD (OR: 1.9 [1.2, 2.9]) but not with IVH (OR: 0.98 [0.58, 1.6]) in the adjusted models.

DISCUSSION

Our findings on the association of low neutrophil count defined as less than 1000/μL with neonatal complications among the entire VLBW NICU population with gestational age less than 32 weeks, in Wisconsin in 2003-2004, are very consistent with previous findings in more selected groups of infants (4). Hence, routine differential blood counts point to subpopulations at higher risk for respiratory complications, as well as for IVH above the mildest level. However, the strength of associations was weak to moderate in previous studies as well as in ours, except possibly in the subgroup with corrected WBC between 5000-7000/μL. Consistent with worse clinical outcomes, infants with low neutrophil counts had less favorable baseline physiologic status as measured by the SNAP-II, The association between low neutrophil count and SNAP-II was also strongest in the 5000-7000/ μL WBC group. For unknown reasons associations with the mildest grade of IVH with low neutrophil count differed from those of higher grades, indicating that low neutrophil count may be associated with IVH severity rather than its presence.

Interest in the neutrophil count as a predictor of neonatal outcome arises from animal research showing that a low number of neutrophils in peripheral blood shortly after birth can be a marker

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for inflammatory processes, as neutrophils migrate to affected organs (1-3). It is also well known that there is an association between a high number of inflammatory cells, neutrophils, and macrophages as well as proinflammatory cytokines in tracheobronchial aspirate of preterm infants who developed BPD (17,18). However, potential other factors that affect peripheral neutrophil count are not well understood (15,19), and probably weaken the association between low neutrophils and clinical outcomes observed in practice. In fact, previous research has labeled a large proportion of low neutrophil counts idiopathic, especially among extremely low birth weight infants (15,19). We found counts to be quite low among all VLBW infants born at less than 32 weeks gestation, but even more so among smaller infants and those born ELBW.

Our results underscore the close association between neutrophil count and total white count. For example, low neutrophil counts are virtually absent when the total count is above 12000/ μL. Yet, neutrophil count, and not total white count predicted IVH and BPD. We believe that this finding supports the neutrophil count as an inflammatory marker but, as indicated above, associations may have been strongly attenuated by the presence of other common but not well described etiologies that affect both total WBC and neutrophil count. For example, infectious processes other than outright sepsis may have counteracted or obscured inflammation related neutrophil migration of neutrophils from the peripheral blood among infants with high white counts, or caused low counts not related to depletion. It is also possible that idiopathic low counts are in some cases the result of reduced production of neutrophil cells from bone marrow (9).

Our results demonstrate that pregnancy complications and therapies affect both the total white count and the neutrophil count. This is consistent with other studies of factors influencing WBC and neutrophil counts (5-7,9). Previous studies of the association between neutrophil count and neonatal outcomes have tended to exclude births following pregnancy complications suspected to affect differential blood counts (4). Interestingly, associations between low neutrophil count, BPD and IVH in this study that excluded key pregnancy complications and infants exposed to antenatal steroids were similar to ours. We found that pregnancy complications lost their association with neutrophil count once white count was taken into account. Hence associations between neutrophil count and pregnancy complications may be mediated through the effects of pregnancy complications on the total WBC.

The mechanisms that affect total white counts shortly after birth also do not appear well understood, however. Infections and inflammatory processes in both the mother and infant are involved (20,21). High white counts in our population appear partly explained by maternal infections, as exposure to PROM and chorioamnionitis were common at high total WBC. Low neutrophil counts were very rare in these groups, however. Sepsis in the infant was most common in the group with the lowest WBC and neutrophil count, and lowest in the group with WBC between 5000 and 7000/ μL, but the incidence was low of early sepsis that could explain the early WBC. The high incidence of later sepsis among those with the lowest white counts is likely due to reverse causation and not unexpected as these infants are susceptible to infection. Furthermore, adjusting for sepsis did not affect the associations between low neutrophil count and neonatal outcomes, despite the fact that sepsis was itself associated with BPD severity. Hence, we found no evidence that infection was a major cause of the association of low neutrophil count with BPD and IVH. Rather, based on differences in association between white count categories, infections may have attenuated the association. Unfortunately, even our large sample size of 1002 VLBW neonates did not yield sufficient power to fully examine differences in associations between neutrophils and outcomes between WBC subgroups.

Infant factors such as race and low birth weight for gestational age have been previously reported to be associated with low neutrophil counts (15). Consistent with recently published work (15), we found an association with SGA and that higher birth weight was protective

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against low neutrophil count. However, we did not find race to be a major factor influencing the counts. Antenatal steroids are well known to have a stimulating effect on leukocyte and neutrophil counts (7) by enhancing the release of neutrophil and decreasing their clearance from the circulation (22). Consistent with this, we found that neutrophil counts were affected by exposure to antenatal steroid therapy. However, antenatal steroid exposure did not affect the associations between neutrophil count and neonatal outcomes.

Our study is unique in having collected information on blood counts as well as clinical characteristics in a statewide population from all level III NICUs. Perhaps, the associations we found are remarkable in light of the variation in blood count practice and causes of low counts that must exist across the spectrum. For example, the timing of the blood samples varied, although all were obtained in the first 2 hours and 29 minutes of life. A more standardized protocol, achievable in an experimental setting may strengthen the association found between neutrophil counts and outcomes. However, the weak to moderate strength of the overall associations, at this point make them more useful for illuminating the etiology of IVH and BPD than for clinical application to predict these outcomes.

Future studies that collect direct inflammatory markers may clarify when low neutrophil counts arise from inflammatory processes associated with neonatal outcomes rather than reflect other etiologies, or conversely when an inflammatory process is not reflected in the neutrophil count.

CONCLUSION

Our findings point to an association between early low neutrophil count in the systemic circulation of premature/VLBW infants early after birth and the development of moderate-severe bronchopulmonary dysplasia and IVH. The associations persist across a wide range of clinical environments and hospital related factors and may underscore an inflammatory process involving early depletion of mature neutrophil cells that migrate into different organs from the peripheral circulation. However, a better understanding of the role of WBC and other factors affecting the neutrophil count is necessary before clinical application.

The Newborn Lung Project involved the following investigators and project and center coordinators

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Table 1

Infant characteristics and pregnancy complications overall and within white count categories as mean (sd) or percent.of column total.

White count/μl:	**All**	**<5000**	**5000 -<7000**	**7000-<12000**	**≥12000**[1]
N all analyzed	1002	277	218	241	266
N ELBW[2]	494	162	85	114	133
Mean (sd)					
Birth wgt (g)***	996 (286)	923 (294)	1052 (267)	1043 (280)	979 (280)
Gestational age (wks)***	27 (2.4)	27 (2.3)	28 (2.4)	28 (2.5)	27 (2.2)
SNAPII score**	19 (15)	20 (15)	17 (15)	18 (14)	22 (17)
% with characteric					
Small for gest. age***	17	29	19	12	6.2
Male	52	57	51	52	46
Black	28	32	26	13	29
PROM***	19	5.4	12	19	41
Chorioamnionitis***	9.3	4.7	5.5	8.6	19
Pregnancy induced hypertension***	20	38	19	15	4.2
Antenatal steroids	77	77	78	73	80
Sepsis in 1st 2 days	4.9	5.1	6.4	4.5	3.7
Sepsis during NICU stay	17	20	14	15	20
Moderate or worse BPD	33	37	28	33	33
Severe BPD	12	13	13	12	9.6
Any IVH	27	23	29	30	27
IVH grade 2 or worse	15	15	15	17	15
IVH grade 3 or worse	9.5	12	6.0	11	8.5
IVH grade 4	5.3	6.1	3.7	6.8	4.2
Neutrophil count<1000/μl***	24	67	17	7.9	0.41
Neutrophil count<1000/μl*** Among ELBW[2]	29	72	19	8.8	0.75
Neutrophil count<1000/μl*** Among non-ELBW	20	59	16	7.2	0

*** p<0.001

** p<0.01

* p<0.05 for difference between white count groups

[1] 26 neonates had white counts above 34,000/μL with a range of 34, 600-117,400/ Five were >60,000, seven were 40,000-55,000 and fourteen were 34, 000-49,000 Neutrophil counts for these neonates were 3,288-58,700/ μL.

[2] ELBW, Extremely Low Birth Weight (≤ 1000g)

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Table 2

Infant characteristics and pregnancy complications overall and by neutrophil count categories as mean(sd) or percent.

Neutrophil count/μl:	**All**	**<1000**	**1000 -<2000**	**2000-<4000**	**≥4000**
N	1002	244	256	247	255
Mean (sd)					
Birth wgt (g)***	996 (286)	907 (305)	1002 (270)	1069 (265)	1006 (279)
Gestational age (wks)***	27 (2.4)	27 (2.3)	28 (2.5)	28 (2.3)	27 (2.3)
SNAP-II score*	19 (15)	22 (16)	18 (16)	17 (13)	20 (16)
% with characteristic					
Small for gest. age***	17	27	23	9.3	7.5
Male*	52	59	51	52	45
Black	28	28	23	28	31
PROM***	19	7.4	9.8	20	38
Chorioamnionitis***	9.3	6.6	4.7	8.1	18
Pregnancy induced hypertension***	20	34	25	13	7.2
Antenatal steroids*	77	73	75	78	84
SNAP-II score*	19 (15)	22 (16)	18 (16)	17 (13)	20 (16)
Sepsis in 1st 2 days	4.9	6.6	2.7	6.9	3.5
Sepsis during NICU stay*	17	23	13	19	16
Moderate or worse BPD**	33	42	29	30	32
Severe BPD*	12	16	10	14	7.9
Any IVH	27	25	26	25	24
IVH grade 2 or worse[1]	16	21	17	13	14
IVH grade 3 or worse**	11	16	9.8	8.1	8.2
IVH grade 4	5.3	8.6	4.3	3.6	4.7

*** p<0.001

** p<0.01

* p<0.05 for difference between neutrophil count groups

[1] p=0.0761 for differences between groups, p=0.0175 for trend

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Table 3

Association of infant outcomes with low neutrophil count (<1000/ μL.). Entries are odds ratios with 95% confidence intervals or difference with 95% confidence interval. Infants with WBC ≥ 12, 000 are excluded.

White count/μL.:	Overall[1] OR 95% CI	<5000 OR 95% CI	5000-<7000 OR 95% CI	7000-<12000 OR 95% CI
SNAP-II unadjusted	6.9*** 4.2- 9.7	5.7** 1.9- 9.6	9.8*** 4.6- 15	6.3 -0.2- 13
SNAP-II adjusted[2]	3.6** 1.4- 5.8	2.3 -0.9- 5.4	6.3** 2.0- 11	4.1 -1.2- 9.5
≥Moderate BPD unadjusted	1.9** 1.1-3.1	1.9* 1.1- 3.4	2.3* 1.0- 5.1	1.4 0.5- 3.9
Severe BPD unadjusted	1.8* 1.0-3.3	1.2 0.6- 2.8	3.2* 1.2- 8.3	1.6 0.4- 5.9
BPD across levels adjusted[2]	1.7* 1.1-2.7	1.7 0.9- 3.1	1.9 0.8- 4.8	1.6 0.5- 5.0
BPD across levels adjusted[3]	1.7* 1.0-2.7	1.5 0.8- 2.8	2.0 0.8- 4.9	1.7 0.6- 5.3
Any IVH unadjusted	1.5 1.0-2.2	1.9 1.0- 3.5	1.6 0.8- 3.4	0.7 0.3- 2.0
≥ grade 2 IVH unadjusted	2.1** 1.2-3.6	2.3* 1.0-5.2	2.9* 1.2-6.8	1. 2 0.4-3.7
≥ grade 3 IVH unadjusted	2.5** 1.3-4-7	2.3 0.9- 5.9	7.3*** 2.3- 23	0.8 0.2- 3.8
grade 4 IVH unadjusted	2.6* 1.2-5.8	4.0 0.9- 18	5.4* 1.3- 23	0.7 0.09- 5.3
IVH across grades 2 to 4 adjusted[2]	2.2** 1.3-3.8	2.7* 1.1- 6.7	3.0* 1.2- 7.4	1.2 0.4- 4.1
IVH across grades 2 to 4 adjusted[3]	2.2 1.3-3.8	2.6* 1.0-6.6	2.9* 1.2- 7.1	1.2 0.4- 4.0

*** p<0.001

** p<0.01

* p<0.05 for significance of association with low neutrophil count.

[1] Overall odds ratios, and SNAP-II difference are adjusted for white count categories included in addition to other variables.

[2] Adjusted for birth weight, gestational age, sex and antenatal steroids.

[3] Adjusted for birth weight, gestational age, sex and sepsis during NICU stay.